'TENORMIN'
atenolol

a comprehensive review

Contents

Introduction

[illegible]

It was another twelve years before this theory was confirmed by the work of Black whose special interest [illegible]

[illegible]

smooth muscle relaxation and decreased blood pressure produced by isoprenaline,[3] might be the key to the development of more therapeutically useful drugs.[2]

The result of further research was the synthesis, in 1960, of pronethalol which inhibited the effects of sympathomimetic amines and sympathetic nervous stimulation on the heart.[4,5] Propranolol followed in 1962 and clinical studies showed it to be effective initially in the treatment of angina During the late 1960s Lands and co-workers[6] further suggested that beta-receptors could [illegible]

[illegible] -receptor [illegible]

Since the introduction of 'Tenormin' into clinical practice in 1976, it has firmly established itself as the world's most widely-prescribed, cardioselective beta-[illegible]

[illegible]

The aim of this book is to comprehensively review the pharmacological properties of 'Tenormin' (the importance of cardioselectivity, hydrophilicity and lack [illegible]

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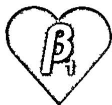
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'Tenormin' The advantages of cardioselectivity



Contents

'Tenormin' – the advantages of cardioselectivity

Clinical relevance of cardioselectivity

Ever since Lands in 1967 proposed the existence of two types of beta-receptor with $beta_1$-receptors occurring predominantly in the heart and $beta_2$-receptors predominantly in the periphery, it has been theoretically desirable for a beta-blocker to possess the property of *cardioselectivity. This is defined as the ability to block preferentially the cardiac $beta_1$-receptors at doses which leave the peripheral $beta_2$-receptors relatively unaffected.* The distribution of some of the main $beta_1$- and $beta_2$-receptors is shown below (Figure 1).

A beta-blocking agent which is non-selective might be expected to confer all the benefits of $beta_1$-blockade but

hypoglycaemia.[1]

Although the property of cardioselectivity is relative rather than absolute, *'Tenormin' is one of the most cardioselective beta-blockers yet to become available for clinical use*

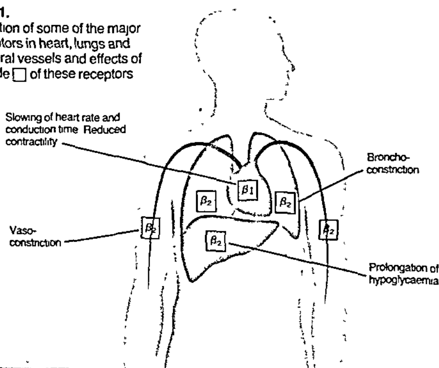


Figure 1.
Distribution of some of the major β-receptors in heart, lungs and peripheral vessels and effects of blockade ☐ of these receptors

This has been demonstrated in a quantitative model in

obstruction and will be described below. They have also been reviewed by Cruickshank [1]

Cardioselective 'Tenormin' has little effect on lung function

Volunteer studies

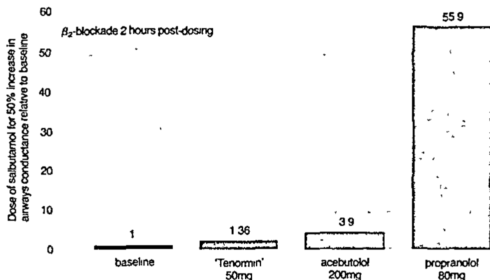
The bronchus represents a clinically relevant

measuring the dose of an inhaled beta-stimulant required to produce 50% of maximal bronchodilator response during treatment with one of several beta-blockers

Studies from this group[2] have shown that the dose of salbutamol required for a 50% increase in airways conductance, relative to baseline, was 41 times greater after 80mg propranolol than after 50mg 'Tenormin' (Figure 2) These two doses produced equivalent beta$_1$-blockade

Using the same model, Harrison and Tattersfield[4] have compared 'Tenormin' with another selective agent,

exerted the same degree of beta$_1$-blockade. However,



"On available evidence atenolol ['Tenormin'] and

The relevance of these studies depends on the

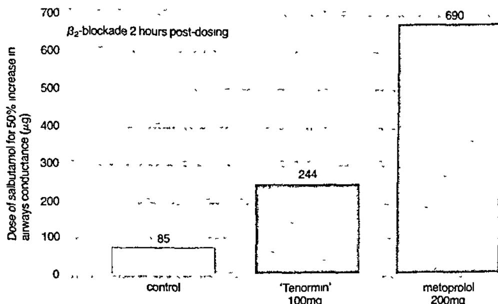
Although this assumption is difficult to prove, the investigators point out that, " .. *clinical studies of oral beta-adrenoceptor antagonists in patients with asthma are in good general agreement with our findings."*[6]

Acute studies in asthmatics

The implications of cardioselectivity for the asthmatic have been illustrated by Benson *et al*[7] They showed that

These patients (termed "*responders*") reacted badly to non-selective beta-blockers whether or not intrinsic sympathomimetic activity (ISA) was present (eg pindolol) In a randomised, crossover comparison of propranolol, pindolol, acebutolol and 'Tenormin' in 12 patients with asthma,[7] bronchoconstriction in the five "*responding*" patients was greatest following propranolol and least following 'Tenormin', the only drug which did not differ significantly from placebo.

Figure 3.
Comparison of 'Tenormin' (100mg) and metoprolol (200mg) on airways function in volunteers 2 hours after dosing[4]



Even more important is the fact that only the cardioselective drugs, 'Tenormin' and acebutolol

These results were confirmed in a similar study[10] in ten asthmatic patients, comparing 'Tenormin', metoprolol,

significantly from placebo (Figure 4). Furthermore,

'Tenormin' was the only drug not to cause wheezing and not to differ from placebo in response to inhaled

studies in patients with airways obstruction by several other workers [11-20]

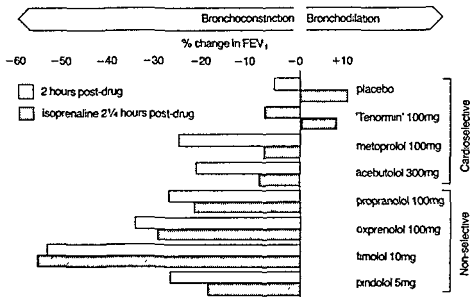
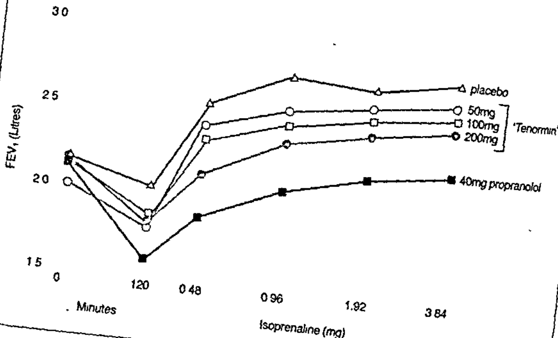


Figure 4.
Effects of β-*blocker* and isoprenaline on FEV_1 *in 10 "responding"* (labile) asthmatic patients[10]

controlled study in ten patients with hypertension and



Chronic studies in asthmatics

Lawrence *et al*[22] compa... doses of ... [illegible]

who ... *inhalant* ... *with a beta*$_2$ ... [illegible]

Table 1. Comparison of 'Tenormin' and metoprolol, given chronically, on respiratory function in asthmatic hypertensives[22]

		Total no. of asthmatic attacks (n=13)	Total no of asthma-free days (n=13) metoprolol	% time with v. severe, severe or moderate wheeze (n=12)
'Tenormin'		244	219	50
metoprolol		298	199	74
placebo		272	217	60
Statistically	MvP	NS	NS	NS
significant	MvT	p<0 05	p<0 05	p<0 05
	TvP	NS	NS	NS

T = 'Tenormin' M = metoprolol P = placebo NS = non-significant

Conclusion

since cardioselectivity is dose-related and a $beta_2$-stimulant should be available for use if indicated

Cardioselective 'Tenormin' and delay of recovery from hypoglycaemia

Diabetic patients show a high prevalence of

reflex bradycardia during hypoglycaemia. The property of cardioselectivity has a marked influence on these potential complications

Duration of hypoglycaemia

agents.

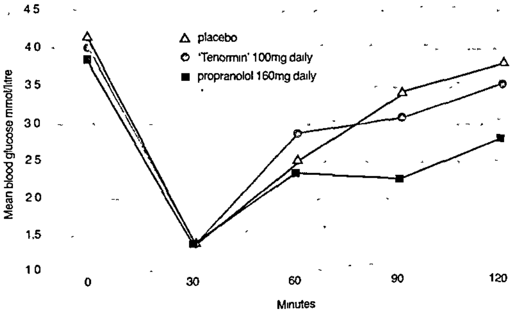


Figure 6.
Effect of 'Tenormin' and propranolol on insulin-induced hypoglycaemia in normal subjects[26]

Signs and symptoms of hypoglycaemia

Acute hypoglycaemia results in the release of several hormones including catecholamines in an effort to

is preserved and this constitutes an important advantage of a selective agent such as 'Tenormin' in diabetics.

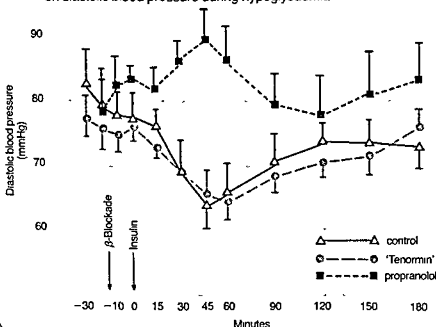


Figure 7.
Comparison of effects of 'Tenormin' and propranolol on diastolic blood pressure during hypoglycaemia[27]

Conclusion

When compared with non-selective beta-blockers, it would appear that a cardioselective beta-blocker such as 'Tenormin' is less likely to delay the recovery from hypoglycaemia and may also be less likely to block the warning signs, eg tremor The lack of diastolic pressor

Cardioselective 'Tenormin' in beta$_2$-vasodilatory-mediated stress situations

Stress situations which increase adrenaline secretion,

Cigarette smoking

The cardiovascular responses to smoking during acute

study.[35] Propranolol, but not 'Tenormin', caused a

the management of patients who are habitual smokers,"[35] (see Footnote, page 16).

In an evaluation of chronic oral drug administration (at least four weeks' treatment with propranolol 160mg

($p<0.0003$) with 'Tenormin' lower than the non-selective

about 15 minutes) and so the initial effect became diluted when the longer time period was considered

Smoking and coffee drinking

(Figure 9).

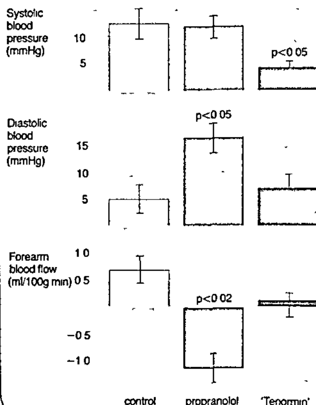


Figure 8.
Haemodynamic changes in 7 habitual smokers following intravenous doses of 'Tenormin' and propranolol[35]

In discussing the practical implications of th

Furthermore "*Beta - selective blockade*

Other recent studies[38,39] have also confirmed the therapeutic advantage of cardioselective drugs such as 'Tenormin' in hypertensives who smoke

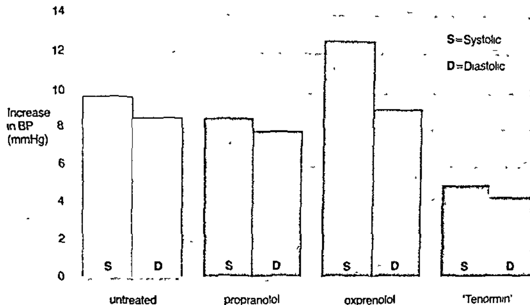


Figure 9.
Mean change in blood pressure from placebo values (orange juice) in 8 hypertensive habitual smokers 5-120 minutes after coffee plus smoking[37]

Conclusion

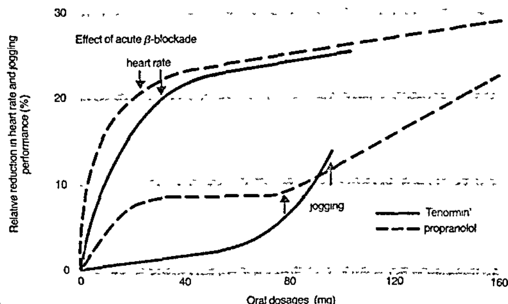
Low-dose cardioselective 'Tenormin' and exercise capacity

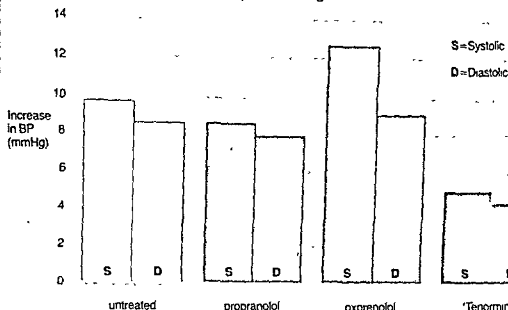
patients

Work from Sweden[40] has shown that long-distance runners have a predominance of slow twitch muscle fibres whereas sprinters have a predominance of fast twitch fibres. In the slow twitch fibre, metabolic

A $beta_2$-component seems likely in this process and

Figure 10.
The effects of short-term non-selective and β_1-selective blockade on jogging in healthy young men[40]





Conclusion

Low-dose cardioselective 'Tenormin' and exercise capacity

patients.

*Longer-term studies carried out by the same workers (ref.35a) suggest that the difference between propranolol and 'Tenormin', seen acutely, may diminish with chronic beta-blockade treatment.

Lipoproteins

Beta-blocker therapy has been associated with an

factor, low-density-lipoprotein (LDL) cholesterol was not consistently affected by beta-blockade and was [illegible] these

relevance of these changes is uncertain, particularly in view of the evidence for a cardioprotective effect of beta-blockade (See 'Myocardial Infarction' chapter)

Summary: 'Tenormin' – the advantages of cardioselectivity

- allows a wide patient selection
- ability to be prescribed, with care, to patients with potential airways problems
- can be prescribed in insulin-dependent diabetics
- may be preferable in hypertensives who smoke and drink coffee
- minimal reduction in physical performance with low dose 'Tenormin'

tolerance. The fatiguing effect of non-selective blockade persisted during training and limited the effect of the training programme to a greater extent than 'Tenormin'.

Conclusion

in physically active hypertensives since, compared with non-selective agents, it interferes less with the various metabolic processes supplying the muscles with energy

The effect of cardioselective 'Tenormin' on other variables

Cold extremities and Raynaud's phenomenon

All beta-blockers cause cold extremities in some patients Marshall *et al*[42] have indicated that this may be less of a

Renal function

Although there is some controversy over the effects of beta-blockers on renal function and renal blood flow, the concensus of opinion seems to be that, at least in the

clearance

this drug. With 'Tenormin' there was no significant

increased by an average of 9% but remained within the

cardioselective agent.

ese

of

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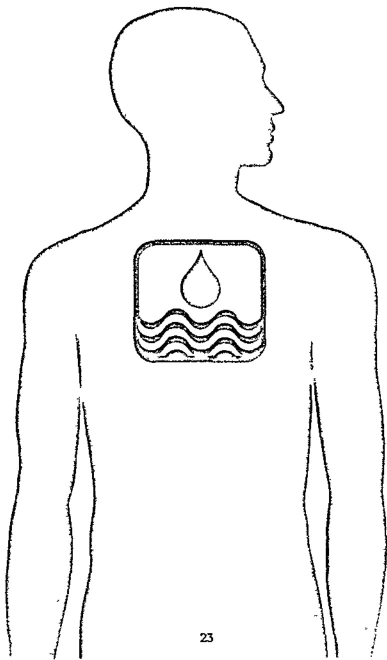
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'Tenormin'
The benefits of hydrophilicity



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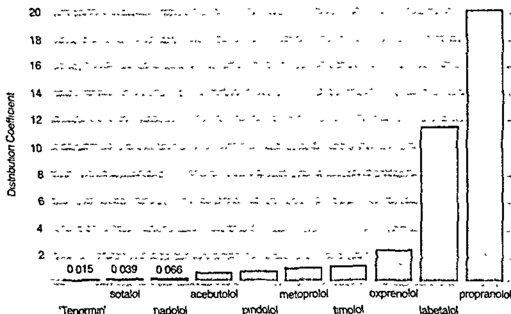
Pharmacokinetics

The hydrophilicity of a beta-blocker relates to its distribution or partition in an octanol/aqueous medium The partition coefficient of a drug is the ratio of its concentration in octanol and water and the lower the value, the more water soluble is the drug

The "distribution coefficient" of a compound is more relevant to biological systems since it also takes into account pH and temperature

Woods and Robinson have calculated the distribution coefficients for most commonly available beta-blockers, the most hydrophilic being 'Tenormin' (Figure 1) [1]

Figure 1.
Distribution coefficients in octanol/aqueous buffer (pH 7 4 and 37°C) for several beta-blockers



Hydrophilicity gives more consistent pharmacokinetics than lipophilic agents

The extent of water-sol

Contents

'Tenormin' – the benefits of hydrophilicity

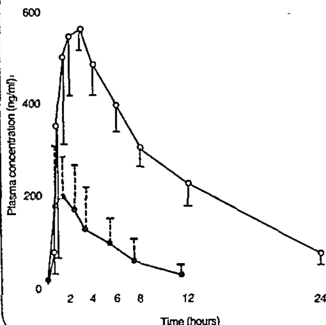


Figure 2.
Plasma metoprolol concentrations over time in extensive (●) and poor (○) hydroxylators of debrisoquine

Long duration of action and once-daily dosing give good antihypertensive control and compliance

However, lipophilic beta-blockers have short plasma half-lives[19] unless used in long-acting formulations.

The longer more predictable pharmacodynamic action of 'Tenormin' can be seen in clinical practice where it produces smooth 24-hour control of blood pressure For

agents metoprolol and pindolol[20] (Figure 3)

kidneys. 'Tenormin' is only found at extremely low levels in the deeper body compartments, such as the brain [2]

Including predictable blood levels

variability in peak 'Tenormin' blood levels is only about

contrast to 'Tenormin' which undergoes only minimal metabolism

Even with impaired liver function

In patients with varying degrees of liver function it has been demonstrated that there was a greater variation in peak plasma levels of metoprolol and propranolol than 'Tenormin' and that the kinetics of 'Tenormin' were independent of the liver [7,8]

The small variability in plasma levels of 'Tenormin' helps to explain its narrow dose range compared with the lipophilic beta-blockers which may require titration to suit individual patient needs

Or with inherent genetic defects in metabolism

Some populations exhibit genetic polymorphism with about 90% being extensive metabolisers of debrisoquine

Further evidence for the superiority of 'Tenormin' over 100 mg metoprolol or 200 mg sustained-release metoprolol was provided by Scott *et al* who showed significantly better blood pressure control over 24 hours with 100 mg 'Tenormin' than either conventional metoprolol or a long-acting formulation [21]

In contrast to the accepted control of hypertension and

prescribed twice-daily in conventional formulations.[23,24]

High compliance with once-daily 'Tenormin'

The predictable clinical response to once-daily 'Tenormin' means that compliance is extremely high. A mean of 92% compliance was reported with 'Tenormin' in one study and this was greater than with conventional propranolol, pindolol, metoprolol or labetalol taken two or three times daily [25] A high compliance rate (76-88%) was also shown by Ingram in a general practice study *involving over 3,000 hypertensive patients* [26]

'Tenormin' offers the advantages of a once-daily dosage with consequent convenience for patients.

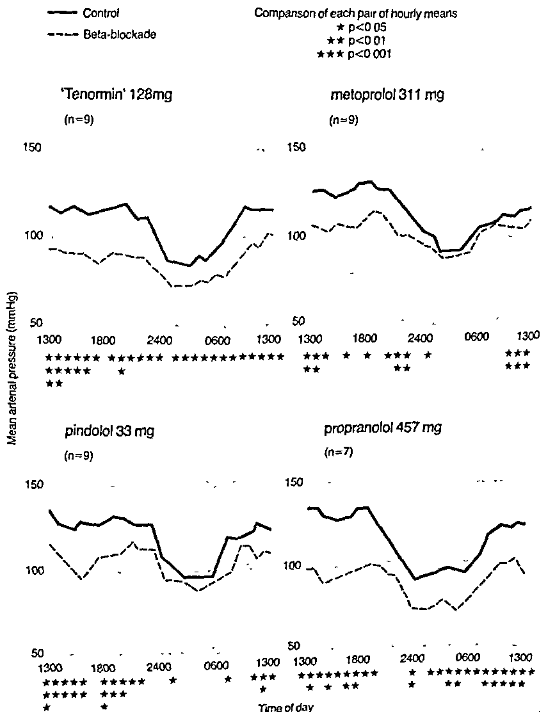
Low distribution coefficient leads to low incidence of CNS-related problems

The volume of distribution of beta-blockers in the various body compartments depends on the

Table 1. Protein binding, lipophilicity and volume of distribution of three beta-blockers.[5,27-29]

Beta-blocker	Plasma protein binding (%)	Hydrophilic/ lipophilic	Volume of distribution (L/kg)
'Tenormin'	3	Very hydrophilic	0.7
metoprolol	10	Lipophilic	5.0
propranolol	90	Very lipophilic	3.6

Figure 3.
Antihypertensive control during 24 hours.
Between-patient comparison of four beta-blockers



Low risk of drug interactions

The water/lipid solubility of a beta-blocker is of

of trials appear in the 'Drug Interactions' chapter

'Tenormin' and psychomotor performance

Widely prescribed drugs such as beta-blockers should not adversely influence patients' abilities to perform everyday tasks involving mental skill or manual dexterity. Many validated tests have been devised in order objectively to measure the effects of drugs on human 'psychomotor performance' (CNS arousal and integration) These tests include critical flicker fusion frequency, simple or complex reaction time, visual

level of alertness or arousal which in turn may be affected by drugs acting on the CNS.

had no adverse effect on reaction times and concentration"[33]

measured using electroencephalograms (EEG), reaction times and critical flicker fusion frequency Vigilance was found to be impaired in hypertensives compared with normotensive controls. 'Tenormin' induced changes in

The hydrophilic nature of 'Tenormin' means that it only reaches the deeper compartments of the body such as the brain with relative difficulty, as shown by the very low concentrations of the drug in the CNS of rats,[30] cats[31] and man.[2]

[illegible]

into the cerebrospinal fluid and brain tissue was [illegible]

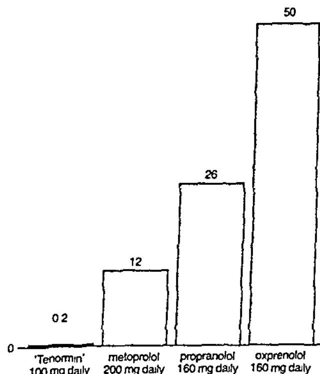


Figure 4.
Brain/plasma ratios of four beta-blockers

Low incidence of CNS side-effects

[illegible] shown that the incidence of CNS [illegible]

Low risk of drug interactions

The water/lipid solubility of a beta-blocker is of

'Tenormin' and psychomotor performance

Widely prescribed drugs such as beta-blockers should not adversely influence patients' abilities to perform everyday tasks involving mental skill or manual dexterity Many validated tests have been devised in order objectively to measure the effects of drugs on human 'psychomotor performance' (CNS arousal and integration) These tests include critical flicker fusion frequency, simple or complex reaction time, visual reaction time, short- or long-term memory, car driving, pursuit rotor and digit-symbol substitution tests The performance of these tasks depends on the individual's level of alertness or arousal which in turn may be affected by drugs acting on the CNS

Many of these tests have also been used to assess the

min'],

measured using electroencephalograms (EEG), reaction times and critical flicker fusion frequency Vigilance was found to be impaired in hypertensives compared with normotensive controls 'Tenormin' induced changes in

Table 2. Effect of 'Tenormin' on various tests of psychomotor function.

Test procedure	Outcome*	References
Reaction time (simple or complex)	−+	33,35,38
Visual reaction time	+	33
Colour/word test	−	40
Critical flicker fusion	−	34,35,38
EEG changes (vigilance)	+	34
Kinetic visual acuity	−+	37,39
Memory (questionnaire)	+	36
Memory (short/long-term)	−	36,38
Digit-symbol substitution test	−	38
Subjective symptoms of.		
arousal	−	39
relaxation	+	32,39
mood	−+	32,39
sedation/drowsiness	−	32,35
sociability	+	38

* − = no change   + = improvement

In trials where the psychomotor effects of 'Tenormin' have been compared with other antihypertensive agents, decrements in psychomotor function were observed with methyldopa.[35] The effects of 'Tenormin' and methyldopa were compared with placebo in two identical studies using simple tests of CNS function [35] One of the conclusions of the trial was that, [illegible]

Other work has also indicated a detrimental effect of methyldopa[36,37] as well as propranolol[38] on psychomotor tests

Effect of 'Tenormin' on driving skills

Driving is one of the most complex psychomotor skills carried out by the average person and requires a good combination of attention, perception and decision

Actual car driving skill was assessed in a double-blind study before and after administration of 'Tenormin',

questions played simultaneously on a tape recorder), driving through a predetermined gap and also

'Tenormin' significantly improved KVA performance

further volunteer study[39] (see Table 2) 'Tenormin' therefore appears to have no adverse effect or may even improve the ability to recognise the hazard from a moving vehicle.

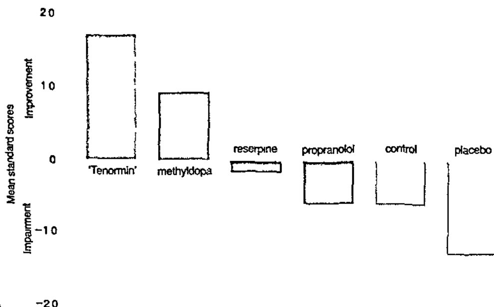


Figure 5.
Kinetic visual acuity – mean standard scores

road driving.[37]

[illegible] mg

relevance to actual car driving is highlighted by the

A driving simulator was used to test the performance of normal volunteers while under mental stress. 'Tenormin' did not impair the subjects performance on this test.[38]

Summary: 'Tenormin' – the benefits of hydrophilicity

- Narrow dose range ensures simple prescribing
- Long duration of action means once-daily dosing and therefore high compliance
- Low penetration into brain results in a very low incidence of CNS side-effects
- Psychomotor performance unaffected or even improved as a result of reduced anxiety

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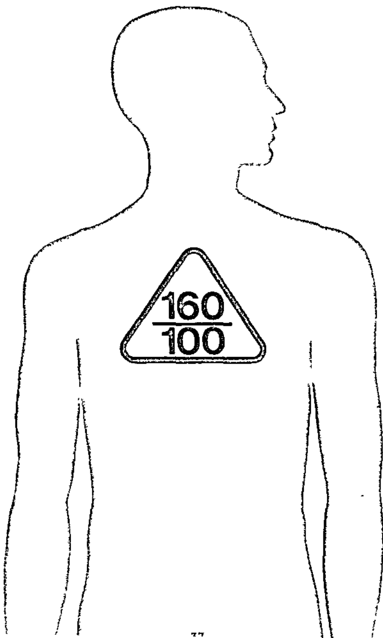
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'Tenormin' in hypertension



Contents

'Tenormin' in hypertension

The increasing role of beta-blockade

Since the first report of an antihypertensive effect by [illegible] in 1964, beta-adrenoceptor blocking agents [illegible]

this area [1,2]

Some general advantages of beta-blockers in hypertension

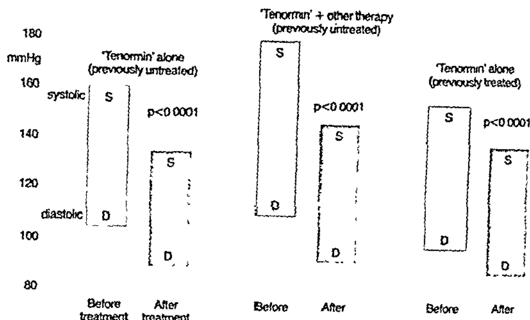
- Evidence for a cardioprotective effect of beta-blockade additional to that of blood pressure control.[3]
- Effective in most grades of hypertension, races and age groups.
- Well tolerated compared with other antihypertensives and with a low incidence of side effects [3]
- Good patient compliance, especially with beta-blockers which can be taken once daily

'Tenormin' – proven antihypertensive efficacy

[illegible]

[illegible]

Hg after treatment with 'Tenormin'.



'Tenormin' compares favourably with other beta-blockers

In 37 published comparative trials of 'Tenormin' monotherapy against other beta-blockers, most comparisons of blood pressure reduction were favourable to 'Tenormin', and it may be concluded that *'Tenormin' is at least as effective as other available beta-blockers in short-term blood pressure reduction, and more effective than most others 20-24 hours after dosing*[6-44] *(Figures 2 and 3).*

Efficacy and tolerance compared with other antihypertensives

Comparison with diuretics

'Tenormin' has been shown in several studies to be more effective than a thiazide diuretic in lowering blood pressure.[8,45-48]

There is a growing body of evidence that long-term diuretic monotherapy for hypertension may cause

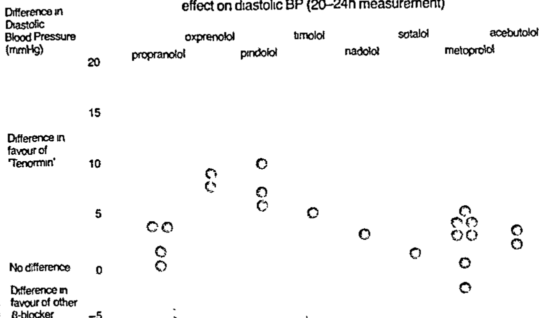


Figure 2. Randomised controlled studies of 'Tenormin' vs. other β-blockers Difference in effect on diastolic BP (20–24h measurement)

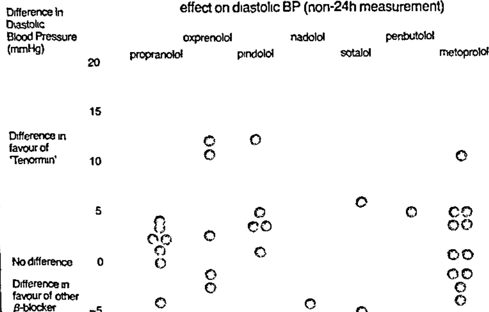


Figure 3. Randomised controlled studies of 'Tenormin' vs. other β-blockers Difference in effect on diastolic BP (non-24h measurement)

significant problems including hypokalaemia, an [illegible]

Professor Dollery has commented that *"The available* [illegible] *beneficial one . . . Beta-adrenoceptor-blocking drugs appear to have the balance of advantage over thiazide diuretics as the first choice when treatment is initiated."*[52]

[illegible] *disturbance, decreased frequency of complaints and* [illegible] is discussed later in the present chapter

Comparison with methyldopa

[illegible] improved blood pressure control with 'Tenormin' as compared with methyldopa, again with a lower incidence of reported problems.[61,62]

Indeed, Magnani concluded from his double-blind randomised comparison that the "*. . . antihypertensive* [illegible]

Comparison with nifedipine

[illegible]

A double-blind crossover study of 35 patients by Daniels and Opie[66] showed that for initial therapy in mild to moderate hypertension, 'Tenormin' was significantly more effective than nifedipine as monotherapy (Figure [illegible] which may be of particular benefit to patients with *resistant hypertension.*

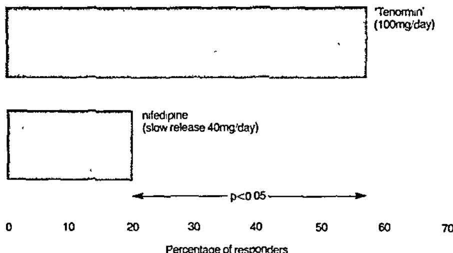


Figure 4. Supine diastolic pressure reduced to less than 90mm Hg with monotherapy (n=35)

Advantages of 'Tenormin' in clinical practice

Flat dose-response curve

[illegible] dose in moderate and established hypertension. Doses in excess of 100mg/day rarely, if ever, give further benefit.[69]

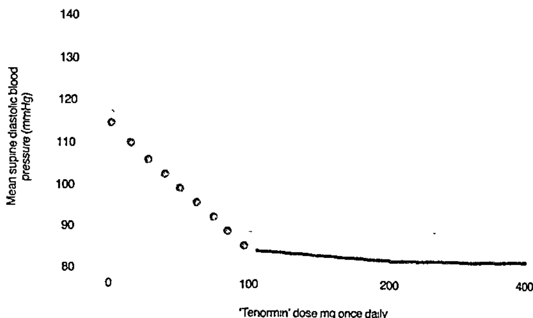


Figure 5. The dose-response curve for 'Tenormin' (n = 16)

Rapid onset of action

'Tenormin' is effective in severe hypertension within 12 hours of the first dose,[71] and some reduction in diastolic blood pressure within 2-3 hours of taking a single 100mg tablet has been reported [72] Fagard found that the major effect was obtained within 48 hours, in contrast to the delay with thiazide diuretics [45] Thus the effectiveness of 'Tenormin' builds up rapidly at first, but approaches a maximum more gradually thereafter

One-tablet-daily dosing

The long half-life of 'Tenormin' and consequent smooth control throughout 24 hours are discussed fully in the 'Pharmacokinetics' chapter

Several investigators have confirmed that 'Tenormin' remains effective in hypertension after several years of continuous use [4,73,74]

Efficacy

The worldwide use of 'Tenormin' now extends to over

The elderly

'Tenormin', alone or in combination, is effective and well tolerated in elderly patients A separate section later in the chapter deals with this aspect.

Renin levels

give consistent support to a connection

Race

more effective A combination of these drugs produced an even greater reduction

It may be that a beta-blocker/diuretic combination is most suitable for black hypertensives because the diuretic eliminates excess plasma volume or sodium concentration, allowing the beta-blocker to act more effectively[76,78]

There is considerable evidence of the effectiveness of 'Tenormin' in hypertensive Asians[59,60,79 81]

Asthmatics

Diabetics

The cardioselective properties of 'Tenormin' make it an appropriate choice of beta-blocker for diabetics at risk of hypoglycaemia (see also 'Cardioselectivity' chapter)

Cigarette smoking and coffee drinking

'Cardioselectivity' chapter)

Combinations with other antihypertensives

Patients may be transferred to 'Tenormin' directly from

50), and free combinations with diuretics or calcium antagonists (eg nifedipine) may be prescribed

'Tenoretic' = 'Tenormin' plus diuretic – well balanced for added response

Combined treatment with 'Tenormin' and a diuretic

A particular advantage of this combination is that some of the biochemical alterations seen with diuretic

compliance

'Tenoretic', containing 100mg 'Tenormin' and 25mg

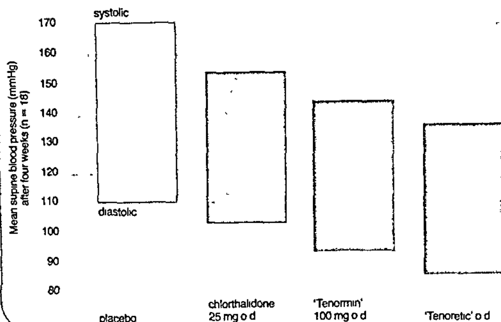


Figure 6. Evaluation of 'Tenormin', chlorthalidone and their combination, 'Tenoretic'

In clinical trials, 'Tenoretic' produced diastolic blood pressures of 95mm Hg or less in about 75% of the patient population [88] There was a low incidence of side-effects[89,90] and the one-tablet-daily regime improved compliance [91]

A post-marketing evaluation of 'Tenoretic' in 6,510

incidence of side-effects, particularly those related to the central nervous system

'Tenoret' 50 – a low-dose combination for hypertension in the elderly

'Tenoret' 50 is the first beta-blocker product to be

patients who are susceptible to side-effects on other therapy or who require simplification of their treatment.

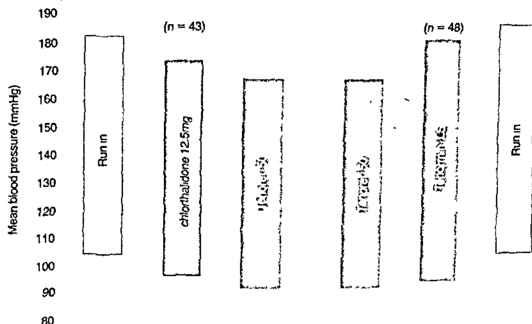


Figure 7. Effect of 'Tenoret' 50 on blood pressure of elderly hypertensive patients

... of hypertension in the elderly particularly

...

therapy is therefore especially critical

'Tenormin' in combination with vasodilators and diuretics

... diuretics and peripheral vasodilators have

...

Hydralazine was the most generally suitable, with prazosin a close second choice Methyldopa was similarly effective but less well tolerated Minoxidil was more effective, but caused fluid retention in more severely hypertensive patients. Labetalol (800-3200mg/

'Tenormin' with methyldopa

A combination of 'Tenormin' (150mg/day) and methyldopa (750mg/day) was found by Wilson[53] to be more effective than either therapy alone and was considered preferable to dosage escalation. Other studies have confirmed this [54,100]

'Tenormin' with calcium antagonists

The addition of nifedipine to 'Tenormin' has been found to give a further fall in blood pressure.[101,102] Compared with nifedipine monotherapy, the combination has also

months on nifedipine [63]

This combination is suitable for patients with normal left ventricular function[102] and does not consistently lead to heart failure in cases of impaired ventricular function [103]

Not only is the depressant effect of verapamil more potent, but it reinforces the effect of beta-blockade in slowing conduction through the AV node This combination is contra-indicated in patients with impaired left ventricular function or conduction defects but is usable and effective in those with healthy hearts [104]

'Tenormin' with clonidine

When combined with non-selective beta-blockers,

vasodilation, and Lilja has confirmed that a combination of 'Tenormin' and clonidine is more effective than clonidine alone [105] If this combination is withdrawn, administration of clonidine should be continued for several days after withdrawing 'Tenormin'

'Tenormin' with ACE inhibitors

There is still insufficient clinical experience with

Other aspects of beta-blockade in hypertension

Regression of left ventricular hypertrophy

angina pectoris

Treatment with 'Tenormin' has been shown to produce regression of left ventricular hypertrophy.[129-131] This effect was unrelated to the degree of reduction of arterial

Beta-blockers and hypertension of pregnancy

The most commonly used treatment for hypertension of

There have been a number of controlled studies of

development being affected is a concern, nevertheless, there has been no report to date implicating 'Tenormin' in fetal malformation

'Tenormin' has been detected in both maternal and umbilical serum indicating transplacental passage of the

rate when administered to patients for hypertension of pregnancy[134,135]

Rubin[136] stated in a review: *"The overall conclusion to be drawn from the present evidence is that beta*

'Tenormin' in hypertension of pregnancy

It should be noted that hypertension of pregnancy is not

with any medication used during pregnancy or lactation, the anticipated benefits of 'Tenormin' must be weighed against possible risks.

Rubin et al[134] *conducted a placebo-controlled study* comparing 'Tenormin' with conventional obstetric management in 120 women developing hypertension in the last trimester

'Tenormin' (100-200mg once daily) significantly reduced blood pressure, tended to prevent proteinuria, and reduced the need for hospital admissions Conventional

'Tenormin' but the systolic blood pressure of the babies was the same in both groups No baby died or had any congenital malformation

'Tenormin' group were developing normally

Conclusions

The overall conclusions of this and other studies may be summarised as follows. 'Tenormin'.–

- Reduces maternal blood pressure effectively with a low *incidence of side-effects* [134,135,137-142]
- Reduces hospital admissions, with its consequent disruption of family life and expense [134]
- Reduces the incidence of respiratory distress

- Reduces the incidence of proteinuria, without masking the presence of this useful sign of fetal distress [134]
- Crosses the placenta [133,138,143] to give a maternal

  effects to the fetus.
- *Accumulates in breast milk (about three times higher* compared with maternal blood) [139,143,144]
  No detrimental effect in breast-fed babies has been reported. [144]
- No consistent effect on fetal heart rate [134,135,141,145] and no fall in neonatal blood pressure.

In summary, 'Tenormin' has been used under close supervision for the treatment of hypertension in pregnancy It has been shown to be effective and no adverse effects on the fetus have been reported

Cardioprotection with beta-blockers

The reduction in mortality associated with beta-blockade during and after myocardial infarction is now well established

... for a general cardioprotective

Study 1 Patients hospitalised with prolonged ischaemic pain were divided into two groups of 90 each, those who had received a beta-blocker up to the time of admission and a matched sample who had not. Myocardial infarction was confirmed in 30 patients on beta-blockers *and in 62 controls (p<0 001) (Figure 8)* [146]

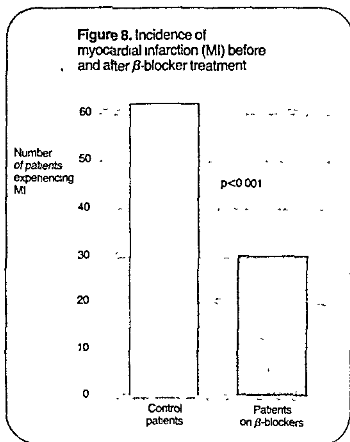


Figure 8. Incidence of myocardial infarction (MI) before and after β-blocker treatment

Study 2 One hundred and sixty-nine severe

infarction were similar.

A similar reduction in blood pressure was achieved in

($p<0.01$) (Figure 9)

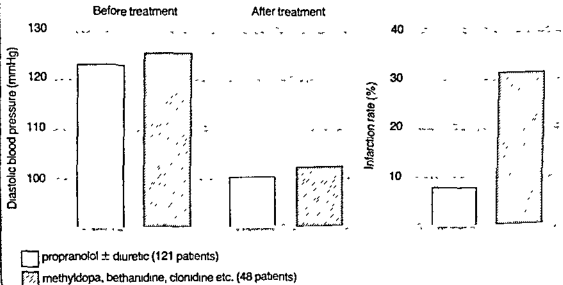


Figure 9. Treatment of hypertension – effect upon occurrence of myocardial infarction (follow-up time up to 5½ years – mean = 2½ years)

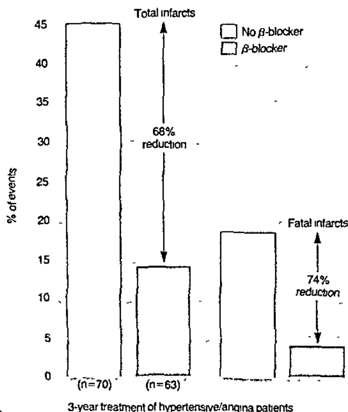
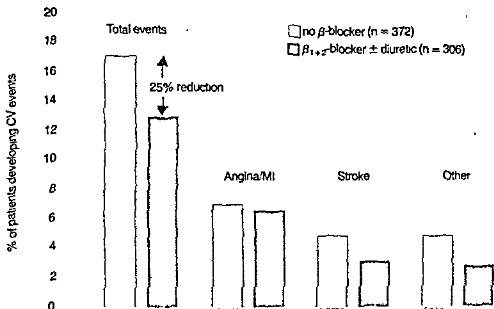
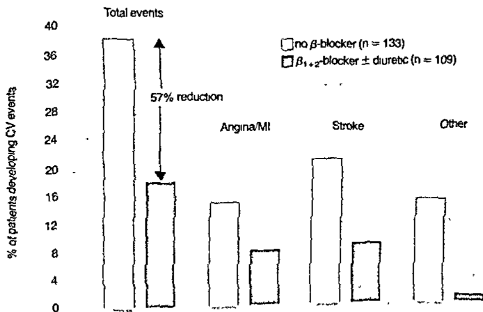


Figure 10. Incidence of myocardial infarctions in 217 patients with angina with or without hypertension

Study 4 The results of treatment in 416 hypertensives

Figure 11. Incidence of cardiovascular (CV) complications in hypertensive patients





Does beta-blockade improve prognosis?

The studies described suggest that beta-blockade may

possible to distinguish between the cardioprotective efficacy of different beta-blockers in uncomplicated

Summary: 'Tenormin' in hypertension

- ○ Proven efficacy in many well-controlled trials
- ○ Low incidence of side-effects in a wide range of patients
- ○ Effective in all races
- ○ Effective in all adult age groups
- ○ Available in strengths and combinations for all grades of hypertension
- ○ Effective in lower dosages when used concomitantly
- ○ Simple one-tablet-daily dosage regime
- ○ Specifically demonstrated to be effective in the elderly with minimal side-effects
- ○ May give a cardioprotective effect not seen with other types of antihypertensive therapy

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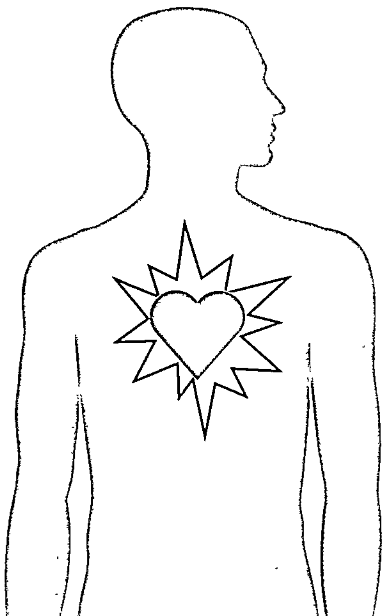
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'Tenormin' in angina



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Angina – a spectrum of clinical conditions

The supply of blood and oxygen to the heart is usually [illegible] discussed in more detail below).

Patients with angina may present with a spectrum of clinical conditions ranging from symptomless (silent) ischaemia along a continuum of worsening symptoms to *the most severe form of ischaemia, myocardial infarction* (Figure 1)

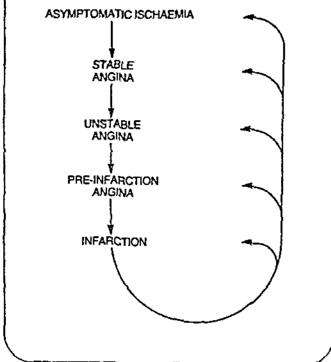


Figure 1.
Ischaemic heart disease continuum

Contents
'Tenormin' in angina

Unstable angina

platelet aggregates, thrombosis or vasospasm. The latter "functional ischaemia" can further complicate effort-or stress-induced angina[10] and S-T segment depression or

frequent, more prolonged or more severe; secondly,

Due to the plethora of terminology used for different

Variant angina

and pain at rest.

'Tenormin' – a first-line therapy in stable angina

The action of *'Tenormin' in angina*

Overall view

populations[1-3] Therefore control of symptoms at an early stage may protect against the consequences of disease progression

Silent ischaemia

Asymptomatic or silent ischaemia is characterised by

of MI or angina.[6]

less than one per cent per year in male office workers[7] *and men with asymptomatic coronary disease without* previous infarction[9] but is worse for patients with additional overt cardiovascular disease.[6]

Stable angina

from ischaemia due to a fixed coronary obstruction or to "functional ischaemia" of varying aetiology (see also below)[10] In the majority of cases, atherosclerosis is the

Stable angina is characterised by pain lasting only a few minutes and which is relieved by rest; S-T segment depression is usually evident

After the onset of uncomplicated angina, the condition may persist unchanged for varying periods, even for

'Tenormin' – effective beta-blockade in stable angina

'Tenormin' was at least as effective as the other beta-blockers as measured by a reduction in anginal attacks, GTN consumption, and an improvement in S-T segment depression and exercise tolerance. In no case was another beta-blocker overall more effective than 'Tenormin'.

Comparison with beta-blockers with ISA

Intrinsic sympathomimetic activity (ISA) refers to the ability of some beta-blockers to stimulate the heart at rest. 'Tenormin' does not have ISA (sometimes known as partial agonist activity or PAA)

sympathomimetic activity Pindolol was shown to

In 19 rigorous studies (all placebo-controlled, double-blind and most of them randomised) including a total of *over 360 patients* and comparing 'Tenormin' with placebo, the overall results presented the same consistent picture [illegible] ischaemia (S-T segment changes) [illegible] 'Tenormin' prove to have an overall detrimental effect on stable angina.

Table 1. Anti-anginal efficacy of 'Tenormin' (100mg/day) **compared with placebo**

Parameter	Percentage improvement*	References
Reduction in anginal attacks	51	21,23-30,32, 33,36-38
Reduction in GTN consumption	46	21,23,29,32, 33,36-38
Improvement in exercise capacity (workload or duration)	32	21,25,27,29, 30,32,34,37
Improvement in exercise S-T changes:		
Severity (mm)	49	21,24,25,28, 30-32,35,37,39
Area (no of positions)	54	25,26,31
Improvement in ambulatory S-T changes.		
Total number	53	25,26,30
Duration (minutes)	57	25,30

*Average of values in studies cited expressed as a percentage

Table 2. Comparison of 'Tenormin' with other beta-blockers

'Tenormin' Dose	Comparator	Study Design (Duration/weeks)	Results: Anginal Attacks	GTN Consumption	Exercise Tolerance	References
25, 50 100mg bd	propranolol 80mg tds	DB (4)	T=Pr	—	T=Pr	21
100, 200mg od 100mg bd	propranolol 160, 320mg/day	DB (4)	T=Pr	T=Pr	T=Pr	50
100, 200mg od 100mg bd	propranolol 80mg bd	DB (3)	T*>Pr	T*>Pr	—	41
100mg od	propranolol 120-320mg/day	SB (4)	T=Pr	T=Pr	T>Pr	51
100mg od	propranolol 240mg/day	DB (1)	T=Pr	—	T=Pr	25
100mg od	pindolol 5mg tds	CO (6) R	T>Pi	T>Pi	T>Pi	47
100mg od	pindolol 5mg tds	DB(5 days)	T>Pi	—	T>Pi	30
100mg/day	pindolol 20mg/day	DB (2)	T=Pi	T=Pi	—	52
100mg od	betaxolol 20mg od	DB (2)	T=B	T=B	T=B	24
100mg od	bisoprolol 10mg od	DB (3)	—	—	T>Bi	34
50, 100 200mg bd	practolol 100 200, 400mg bd	DB (2)	T>Pa	T>Pa	T=Pa	23

DB=double blind, SB=single blind, R=randomised, CO=cross over, T='Tenormin', Pr=propranolol, Pi=pindolol, Pa=practolol, B=betaxolol, Bi=bisoprolol, *'Tenormin' 100mg bd

Both clinical trials highlighted the superior ability of 'Tenormin' to reduce heart rate at rest and during

Retrospective pooled analysis of

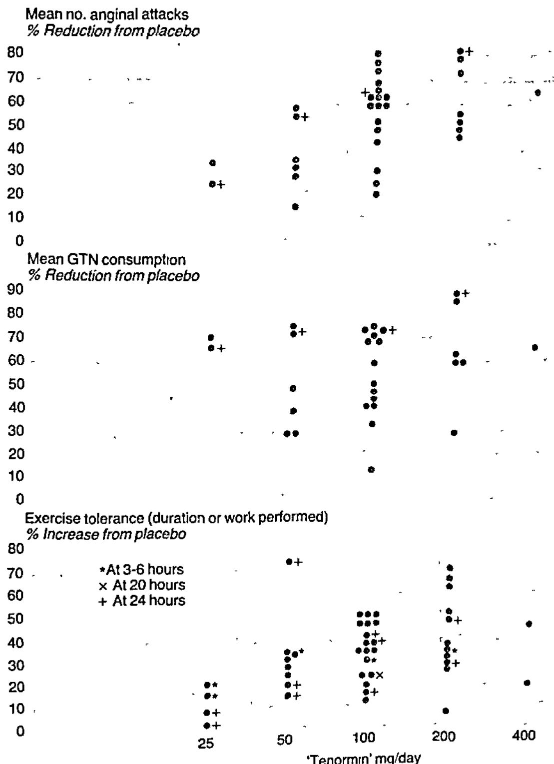

Figure 2. Anti-anginal efficacy in relation to dose of 'Tenormin' compared with placebo [19,21-30,32 34,36-38,43,44,46-49]
Mean no. anginal attacks
% Reduction from placebo
80
70
60
50
40
30
20
10
0
Mean GTN consumption
% Reduction from placebo
90
80
70
60
50
40
30
20
10
0
Exercise tolerance (duration or work performed)
% Increase from placebo
80
70
60
50
40
30
20
10
0
*At 3-6 hours
× At 20 hours
+ At 24 hours
25
50
100
200
400
'Tenormin' mg/day

Table 2. Comparison of 'Tenormin' with other beta-blockers

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Results: Anginal Attacks	Results: GTN Consumption	Results: Exercise Tolerance	References
25, 50 100mg bd	propranolol 80mg tds	DB (4)	T=Pr	—	T=Pr	21
100, 200mg od 100mg bd	propranolol 160, 320mg/ day	DB (4)	T=Pr	T=Pr	T=Pr	50
100, 200mg od 100mg bd	propranolol 80mg bd	DB (3)	T*>Pr	T*>Pr	—	41
100mg od	propranolol 120-320mg/ day	SB (4)	T=Pr	T=Pr	T>Pr	51
100mg od	propranolol 240mg/day	DB (1)	T=Pr	—	T=Pr	25
100mg od	pindolol 5mg tds	CO (6) R	T>Pi	T>Pi	T>Pi	47
100mg od	pindolol 5mg tds	DB(5 days)	T>Pi	—	T>Pi	30
100mg/day	pindolol 20mg/day	DB (2)	T=Pi	T=Pi	—	52
100mg od	betaxolol 20mg od	DB (2)	T=B	T=B	T=B	24
100mg od	bisoprolol 10mg od	DB (3)	—	—	T>Bi	34
50, 100 200mg bd	practolol 100 200, 400mg bd	DB (2)	T>Pa	T>Pa	T=Pa	23

DB=double blind, SB=single blind, R=randomised, CO=cross over; T='Tenormin', Pr=propranolol, Pi=pindolol, Pa=practolol, B=betaxolol, Bi=bisoprolol, *'Tenormin' 100mg bd

Both clinical trials highlighted the superior ability of 'Tenormin' to reduce heart rate at rest and during exercise and consequently, control angina symptoms more than pindolol[30,47]

Retrospective pooled analysis of

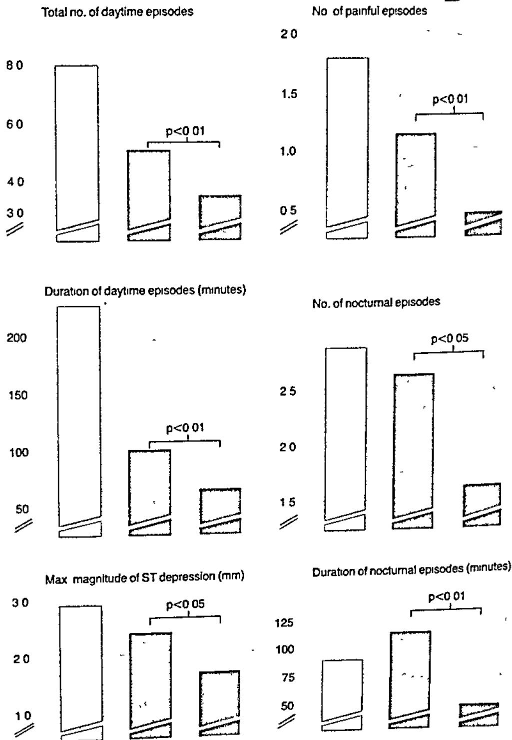


Figure 3. Frequency, magnitude and duration of ST segment depression before and after treatment

also highly effective in cases of angina where ischaemia was caused by stimuli other than an increase in heart

episodes by 78% (Figure 4).[60] Other ischaemic periods were preceded by an increased heart rate, as other workers have also demonstrated[30,61] and in this group of patients, 'Tenormin' reduced the number of episodes by 38%[60] (Figure 4)

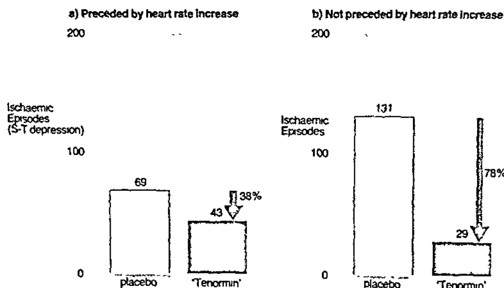


Figure 4. Effect of 'Tenormin' on ischaemia during daily activities (48 hour ambulatory monitoring)

The importance of cardioselectivity

The benefits of hydrophilicity

'Tenormin' (100 mg od) has been compared with an equipotent beta-blocking dose of the lipophilic beta-blocker, propranolol (angina patients previously stabilised on long-term dosage of 120-320 mg/day in divided doses). 'Tenormin' was at least as effective at this level, and significantly better when exercise capacity and ischaemic S-T changes were analysed.[51]

Other studies also indicated that 'Tenormin' has similar efficacy to propranolol in angina [21,41,50]

In a further double-blind, placebo-controlled study, 'Tenormin' and propranolol, in equipotent doses,

the results are given later in this chapter.

Blood levels of 'Tenormin' were unaffected by smoking

Interactions' chapter.

'Tenormin' – a more effective first-line therapy than calcium antagonists in stable angina

Using standard objective methods of assessing the effects

verapamil were equally effective in patients with stable angina[33,35,64 68] (Table 3)

Comparison with *nifedipine*

During exercise testing in one of the studies, 'Tenormin'

of pain, after 'Tenormin' than after nifedipine or placebo (Figure 7)[25] This study also compared 'Tenormin' with propranolol and the results are given earlier in this chapter

These trials showed that 'Tenormin' was more effective than nifedipine in controlling angina (Table 3)

Comparison with nifedipine in habitual smokers

Two published trials comparing 'Tenormin' with nifedipine have included an investigation of the effects of smoking on angina therapy

The double blind trial by Fox and colleagues[25,62] of

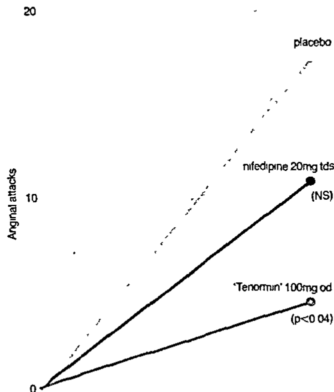
patients continued to smoke and received the drug treatments (including propranolol – see earlier in

Table 3 Comparison of 'Tenormin' with calcium antagonists

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Results				References
			Anginal Attacks	GTN Consumption	Improvement S-T changes	Exercise tolerance	
100mg od	nifedipine 10mg tds	DB (4)	T=N	T=N	—	T=N	42
100mg od	nifedipine 20mg tds, T+N	DB(3)	T>placebo N=placebo T+N>placebo	T>placebo N=placebo T+N>placebo	—	—	38
100mg od	nifedipine 60mg/day	DB (4)	T>N	—	—	T>N	25
100mg/day	nifedipine 20mg tds verapamil 120mg tds, T+N, T+V	DB (3)	—	—	T+N>placebo T>placebo N≥placebo T+V>placebo V>placebo	—	35
100mg/day*	nifedipine 20mg tds*, 40mg bd(LA)*	DB (2)	variable response	—	—	variable response	63
100mg/day	nifedipine 20mg tds, verapamil 120mg tds, T+N, T+V	DB(2)	—	—	T=V T>N	—	64
100mg od	nifedipine 20mg tds, T+N	DB(3)	—	—	T+N>placebo T>placebo N≥placebo	T+N>placebo T>placebo N=placebo	31
100mg/day	nifedipine 10-20mg tds, ISMN 40mg bd	DB (5 days)	T=N T>ISMN N=ISMN	—	T≥N T>ISMN N=ISMN	T=N T>ISMN N=ISMN	61
100mg od*	nifedipine 20mg tds*, propranolol 160mg bd + nifedipine 20mg tds	R (2) CO	P+N=T+N	—	P+N=T+N	—	65
100mg/day	verapamil 120mg tds, T+V	R (6) CO	T+V>placebo T/V>placebo	T+V>placebo T/V>placebo	—	T+V>placebo T/V>placebo	68
50mg bd*	verapamil 120mg tds*, propranolol 80mg bd + verapamil 120mg tds	R (4) CO	T+V=P+V	T+V=P+V	—	—	66
100mg od	diltiazem 60mg tds	DB (6)	(T=D)> placebo	(T=D)> placebo	—	(T=D)> placebo	33
200mg/day	diltiazem 240mg/day	SB (2)	—	—	T>D	(T=D)> placebo	67
100mg od	nicardipine 30mg tds	DB(4)	T=Nic	—	T=Nic	T=Nic	69

T='Tenormin', N=nifedipine, V=verapamil, Nic=nicardipine, LA=long-acting, *=in combination, ISMN=isosorbide mononitrate, D=diltiazem, P=propranolol, DB=double blind, SB=single blind, R=randomised, CO=cross over

Figure 5.
Mean number of anginal attacks during 3-week treatment periods



The investigators commented, " . *atenolol ['Tenormin'] produced a significantly greater reduction than did nifedipine in the frequency of angina and the severity of ST-segment depression on the exercise test*"[25]

Table 3 Comparison of 'Tenormin' with calcium antagonists

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Results: Anginal Attacks	GTN Consumption	Improvement S-T changes	Exercise tolerance	References
100mg od	nifedipine 10mg tds	DB (4)	T=N	T=N	—	T=N	42
100mg od	nifedipine 20mg tds, T+N	DB(3)	T>placebo N=placebo T+N>placebo	T>placebo N=placebo T+N>placebo	—	—	38
100mg od	*nifedipine* 60mg/day	*DB (4)*	*T>N*	—	—	T>N	25
100mg/day	nifedipine 20mg tds, *verapamil* 120mg tds, T+N, T+V	DB (3)	—	—	T+N>placebo T>placebo *N≥placebo* T+V>placebo V>placebo	—	35
100mg/day*	nifedipine *20mg tds**, 40mg bd(LA)*	DB (2)	variable response	—	—	variable response	63
100mg/day	nifedipine 20mg tds, *verapamil* 120mg tds, T+N, T+V	DB(2)	—	—	T=V T>N	—	64
100mg od	nifedipine *20mg tds,* T+N	DB(3)	—	—	T+N>placebo *T>placebo* N≥placebo	T+N>placebo *T>placebo* N=placebo	31
100mg/day	nifedipine 10-20mg tds, *ISMN 40mg bd*	DB (5 days)	T=N T>ISMN *N=ISMN*	—	T≥N T>ISMN *N=ISMN*	T=N T>ISMN *N=ISMN*	61
100mg od*	nifedipine 20mg tds*, propranolol *160mg bd +* nifedipine 20mg tds	R (2) CO	P+N=T+N	—	P+N=T+N	—	65
100mg/day	verapamil *120mg tds,* T+V	R (6) CO	T+V>placebo *T/V>placebo*	T+V>placebo *T/V>placebo*	—	T+V>placebo T/V>placebo	68
50mg bd*	verapamil 120mg tds*, *propranolol* 80mg bd + verapamil 120mg tds	R (4) CO	T+V=P+V	T+V=P+V	—	—	66
100mg od	diltiazem 60mg tds	DB (6)	(T=D)> placebo	(T=D)> placebo	—	(T=D)> placebo	33
200mg/day	diltiazem 240mg/day	SB (2)	—	—	T>D	(T=D)> placebo	67
100mg od	nicardipine 30mg tds	*DB(4)*	*T=Nic*	—	T=Nic	T=Nic	69

T='Tenormin', N=nifedipine; V=verapamil, Nic=nicardipine, LA=long-acting, *=in combination, ISMN=isosorbide mononitrate, D=diltiazem, P=propranolol, DB=double blind, SB=single blind, R=randomised, CO=cross over

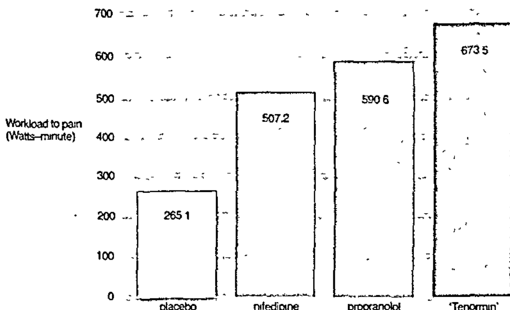


Figure 7.
Workload to onset of chest pain with maximal exercise

In a further study, using higher doses of 'Tenormin' (200mg/day) and diltiazem (240mg/day), both drugs were equally effective in improving exercise tolerance (Table 3) Furthermore, 'Tenormin' produced significantly more improvement in S-T segment depression than diltiazem [67] It was concluded that, ". ['Tenormin'] *has greater anti-ischaemic activity than diltiazem* "

Comparison with nicardipine

[illegible]

Comparison with verapamil

Lessem[68] assessed monotherapy with verapamil (360m...

[illegible]

In a second study of 15 patients with stable angina pectoris, 'Tenormin' (100mg/day) and verapamil (120mg tds) significantly ameliorated exercise-induced S-T segment depression to an equal extent[35,38] (Table 3)

Comparison with diltiazem

'Tenormin' (100mg od) and diltiazem (60mg tds) were

[illegible]

between the two treatments.

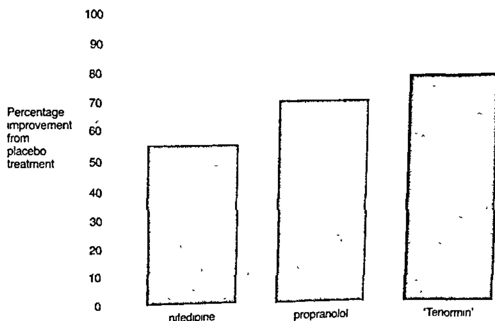
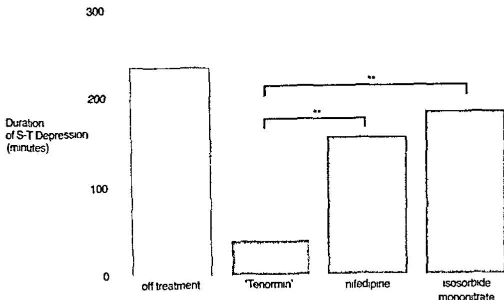


Figure 6.
Improvement in S-T segment depression in stable angina



The investigators concluded *"Overall beta receptor* [illegible]

patients became asymptomatic on 'Tenormin' alone and a further 27% responded to 'Tenormin' in combination with calcium antagonists and other anti-anginal drugs The authors commented *"The administration of atenolol ['Tenormin'] proved to be clinically efficient without left ventricular failure in two-thirds of the patients during hospitalisation and at mid-term follow-up"*[80]

More effective than pindolol

Fifteen patients were included in a double-blind, randomised comparison of 'Tenormin' with pindolol (see earlier section in this chapter)[30] About half of the patients had unstable angina occurring at rest and on effort and the remainder on effort alone. Analysis of all

'Tenormin' – an effective treatment in unstable angina

[illegible]

adrenergic blockade therapy if the latter does not appear to be immediately effective."[74]

[illegible]

increase vascular resistance (due to unopposed α-mediated vasoconstriction) and exacerbate spasm [79]

[illegible]

Overall more effective than nifedipine and ISMN

Newer evidence has demonstrated that 'Tenormin' is *indicated in patients with severe angina occurring on* effort and during the night and which may be the result of severe coronary artery disease.[61] In a double-blind, randomised, cross-over study, nine patients with this [illegible] 'Tenormin' (100mg od), [illegible] ent were assessed by ambulatory ECG monitoring and exercise testing

[illegible] to the onset of ischaemia [illegible]

spasm – however, beta-blocker treatment did not exacerbate his condition [61]

[illegible]

ischaemic episodes was also reduced more by 'Tenormin' than either of the other two treatments (Figure 9) [61]

Few trials have compared 'Tenormin'/nifedipine with other beta-blocker/nifedipine combinations. 'Tenormin'/nifedipine was about as effective as other combinations[65]

'Tenormin'+verapamil

Monotherapy with verapamil (360mg daily) or

was significantly longer than on monotherapy (p<0.01) and GTN consumption was significantly lower (p<0 01) than baseline.

Other studies have confirmed that addition of verapamil to 'Tenormin' produces an additional reduction in S-T segment depression and provides good control of

particularly in patients with conduction abnormalities or impaired ventricular function (see Prescribing Information)

Benefits of 'Tenormin' in angina

Stable and unstable angina

'Tenormin' is a recognised first-line treatment of stable

Long-term treatment

The clinical value of 'Tenormin' in

patients showed that 'Tenormin' was significantly

Coadministration of calcium antagonists and 'Tenormin' in unstable angina

'Tenormin'+nifedipine



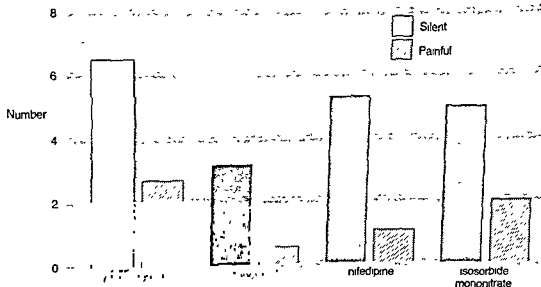


Figure 9.
Comparative anti-anginal efficacy of 'Tenormin', nifedipine and ISMN (silent and painful episodes)

Cardioprotective effect of beta-blockers in angina

be an important advantage in an anti-anginal drug

Weissberg[81] has postulated how beta-blockers may break the link between ischaemia and irreversible

the reduction of infarct size and incidence of arrhythmias [58]

A study reported in 1986 has provided additional evidence in support of a cardioprotective effect of beta-blockade in patients with more serious unstable

their combination on the incidence of recurrent ischaemia or MI within 48 hours of treatment.

Metoprolol alone and metoprolol with nifedipine were the only treatments which resulted in a

protecting against further ischaemia.[82]

Nifedipine administered alone resulted in a trend

Simple once-daily dosage

The optimum dose and frequency have been investigated in a number of blind cross-over studies

Studies have generally shown that 'Tenormin' gives effective control of angina throughout 24 hours, and that twice-daily dosing gives no further advantage over once-daily dosing in almost all patients [19,21,28,32,40,41,44,50,54,57] Some physicians have concluded that, ". . *the 24-hour beta-blocking effect of ['Tenormin'] might be*

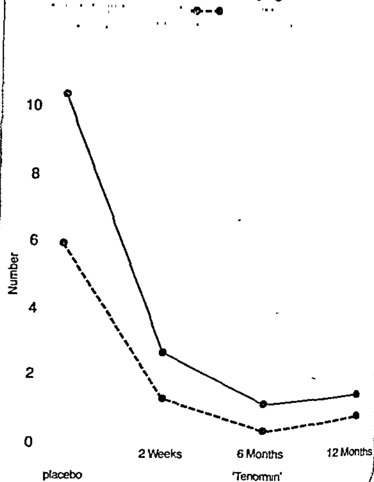


Figure 10.

improvement was not the result of any formal exercise training effect [48]

Cardioprotective effect of beta-blockers in angina

be an important advantage in an anti-anginal drug

Weissberg[81] has postulated how beta-blockers may break the link between ischaemia and irreversible

arrhythmias [58]

A study reported in 1986 has provided additional evidence in support of a cardioprotective effect of beta-blockade in patients with more serious unstable angina [82] This double-blind, placebo-controlled, randomised, multicentre study was designed to determine the effect of metoprolol, nifedipine and their combination on the incidence of recurrent ischaemia or MI within 48 hours of treatment.

Metoprolol alone and metoprolol with nifedipine were the only treatments which resulted in a

Nifedipine administered alone resulted in a trend towards a worse outcome such that the study was stopped prematurely, " . *it was felt unethical to continue nifedipine monotherapy trial medication* "[82]

Simple once-daily dosage

The optimum dose and frequency have been investigated in a number of blind cross-over studies

Some physicians have concluded that, " .. *the 24-hour beta-blocking effect of ['Tenormin'] might be*

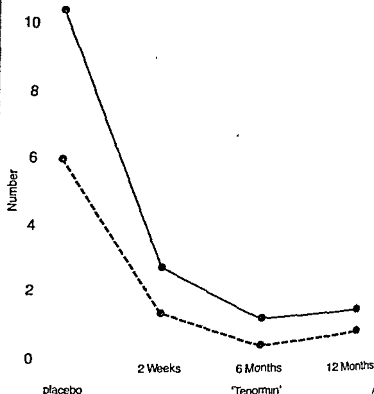


Figure 10. Frequency of angina (●—●) and glyceryl trinitrate consumption (●--●) during placebo and early and long-term 'Tenormin' treatment

months.[48]

During the next nine months, the anti-anginal effect, as represented by these measures, remained constant and

training effect

Schwartz concluded that, *"The beneficial effects of*

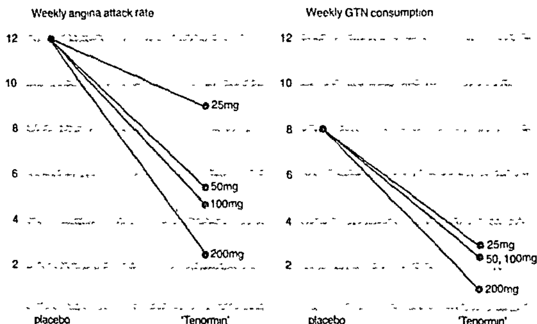


Figure 12. Effect of different doses of 'Tenormin' on angina in 10 patients

Summary: 'Tenormin' in angina

- Effective prophylaxis in classical angina of effort
- Effective in unstable angina occurring at rest and on effort
- [illegible]
- Overall, more effective than nifedipine as monotherapy
- Addition of calcium antagonists can provide extra benefit in severe or unstable angina
- Cardioprotective beta-blockade benefits the patient at risk from MI or sudden death
- Proven long-term efficacy
- Simple once-daily dose for most patients
- Low level of side-effects

Figure 11.
Myocardial infarction or recurrent ischaemia within 48 hours

(No prior β-blockade n=338)

Event Rate %

100

50

24%

20%

placebo

nifedipine

metoprolol

nifedipine + metoprolol

other

100mg/day – optimal in most cases

Most investigators agree that the optimum dose is

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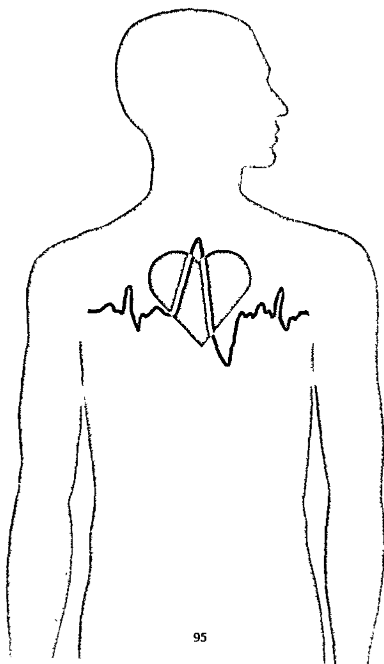
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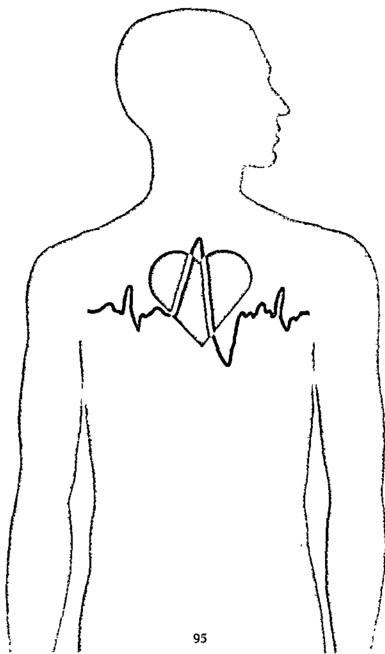
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'Tenormin' in the treatment of arrhythmias



'Tenormin' in the treatment of arrhythmias



Contents

'Tenormin' in the treatment of arrhythmias

Anti-arrhythmic effects of beta-blockade

Beta-blockers are effective anti-arrhythmic agents eg when excessive sympathetic stimulation results in sinus tachycardia and ectopic pacemaker activity Beta-blockade overcomes this by:

- depressing excitability and automaticity
- slowing heart rate
- prolonging refractory period
- depressing conductivity
- preventing ischaemia

The importance of more controversial properties of beta-blockers, such as membrane stabilising activity (MSA), is unclear For instance, practolol, with no MSA, has proven anti-arrhythmic action whereas dextropropranolol, which has MSA properties, has no anti-arrhythmic action [1]

In the opinion of Scheidt, "*Beta-blockers are . .*

[illegible]

Consistent electrophysiological properties of 'Tenormin'

[illegible]

reduction in heart rate), sinus node recovery time,

[illegible]

retractory period of the ventricle.[3,4]

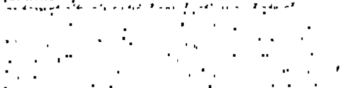
In contrast to other commonly used beta-blockers, 'Tenormin' has been shown to have a wider range of favourable electrophysiological properties[5] (Figure 1)

Figure 1. Electrophysiological properties of β-blockers (investigations in man)

	'Tenormin'	metoprolol	propranolol	pindolol	oxprenolol	acebutolol
Sinus cycle length	○	○	○	○	○	○
Sinus node recovery time	○	ns	nr	ns	ns	ns
SA conduction time	○	○	nr	ns	○	nr
Atrium effective refractory period (ERP)	○	ns	○	○	ns	ns
Atrium functional refractory period (FRP)	○	ns	nr	○	ns	nr
AV node ERP	○	nr	○	nr	nr	nr
AV node FRP	○	○	○	○	○	○
AV node conduction time	○	○	○	○	○	○

○ = significantly prolonged; ns = not significant; nr = not reported

Di-Biase and co-workers concluded that, " *'Tenormin' possesses electrophysiologic properties similar to those of most previously studied beta-blocking agents except for a more pronounced action on sinus node*



AV node re-entrant supraventricular tachycardias."

Furthermore, "*. . the lack of adverse effects on infra-His conduction allows its use also in subjects with intraventricular conduction disturbances.*"[4] However, caution may be necessary in patients with sinus dysfunction (see also Prescribing Information)

Therapeutically-desirable effect on supraventricular arrhythmias

Pacing-induced arrhythmias

tachycardias in 68% of patients by normalising ventricular rate [6]

significance of the results still require to be evaluated

Supraventricular arrhythmias

Four studies described the successful use of intravenous or oral 'Tenormin' in patients with supraventricular arrhythmias such as paroxysmal supraventricular

atrial flutter or atrial fibrillation responded partially or fully to 'Tenormin' whilst 33% of patients with

Additional benefit derived from 'Tenormin' treatment included stabilisation or favourable reduction in blood pressure, resolution of symptoms of heart failure secondary to arrhythmias [10] and a significant fall in heart rate [9]

*As defined by the investigator

Many arrhythmias controlled by standard 'Tenormin' doses

Dose regime and onset of action

Effective doses of 'Tenormin' varied between studies, for instancc
0.1 mg/
min.[10]
50-150mg/day.[9]

Following intravenous administration of 'Tenormin', the anti-arrhythmic action was observed after two minutes, stabilised after 5-10 minutes and remained constant for a minimum of two hours [10] On the other hand. the effect of oral treatment developed more gradually over 24 hours.[10]

Most patients' arrhythmias were satisfactorily controlled on standard 'Tenormin' dose regimes although occasionally the higher doses were required with or without concomitant lignocaine therapy [7]

A well-tolerated treatment for ventricular arrhythmias

Ventricular arrhythmias require careful treatment mainly

infarction.[2]

Several clinical studies have been conducted in which 'Tenormin' was administered intravenously and/or orally

ventricular flutter.[7,10-14]

Extrasystoles

In three studies, oral and intravenous administration of 'Tenormin' resulted in a complete or partial response

patients [11]

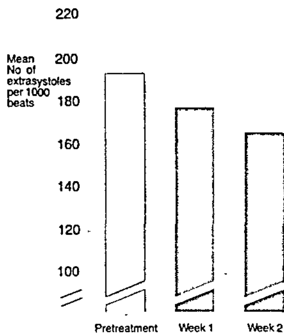


Figure 2. Effect of 'Tenormin' on ventricular extrasystoles

Ectopic beats

Ventricular ectopic beats are presented in approximately 80% of post-infarction patients and indicate an increased risk of cardiac mortality.[14] It is thought that beta-blockers may reduce the incidence of sudden death by preventing ventricular fibrillation and ectopic beats.[14]

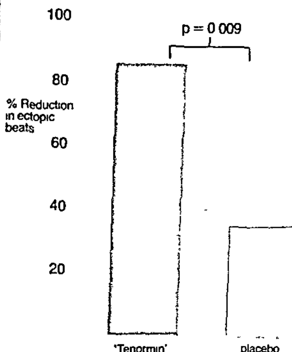


Figure 3. Effect of 'Tenormin' on ventricular ectopic beats

This was further confirmed by the same clinicians in a randomised comparison of 'Tenormin' with prajmalium bitartrate in which 'Tenormin' and prajmalium reduced ventricular ectopic beats by 91% and 77% respectively.

Other ventricular arrhythmias

Other arrhythmias which 'Tenormin' has been shown to control include paroxysmal ventricular tachycardia and ventricular flutter (100% of cases reported),[7] ventricular couplets (71%)[11] and ventricular tachycardia (40%)[11]

Arrhythmias associated with myocardial infarction

Rationale for beta-blockers

It is well accepted that certain beta-blockers are effective

death

It has been postulated that immediate treatment with an anti-arrhythmic agent, such as a beta-blocker, should be instituted. Several non-randomised studies have shown

Trial (BHAT), there was a significant decrease in the number of premature ventricular beats[20] and a small but non-significant decrease in ventricular ectopic activity[21] after oral beta-blockade compared with placebo

Combined intravenous and oral 'Tenormin' for effective control of post-infarction arrhythmias

Supraventricular arrhythmias

Yusuf and co-workers conducted a randomised study in 477 post-infarction patients who presented within 12

discharged

'Tenormin' significantly reduced the

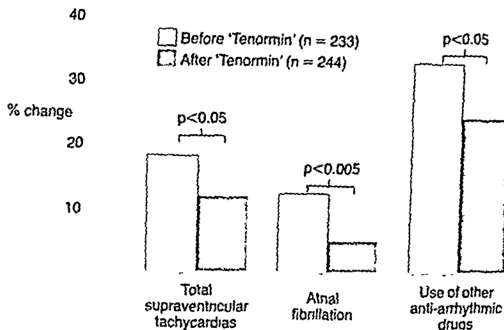


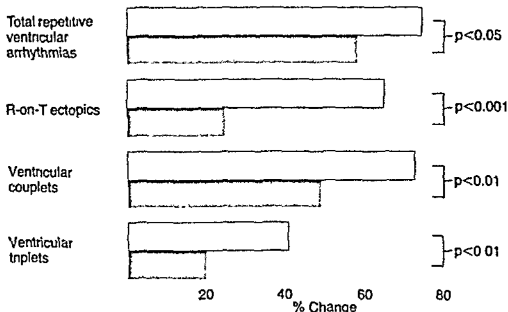
Figure 4. Effect of 'Tenormin' on post-infarction supraventricular arrhythmias

Ventricular arrhythmias

In the same study described above, Yusuf et al monitored ventricular arrhythmias using 24-hour

'Tenormin' provided effective control of the majority of the observed arrhythmias (Figure 5), with equivocal results on ventricular tachycardias.[15,22] For example, 'Tenormin' induced a fall in mean heart rate, reduced the mean (24 hour total) number of ventricular ectopic beats ($p<0.001$); reduced the incidence of R-on-T ventricular ectopic beats ($p<0.001$), reduced the incidence of

'Tenormin' (n=5)



Summary: 'Tenormin' in the treatment of arrhythmias

- Effective in a wide range of arrhythmias
- Unlike many other beta-blockers including other cardioselective agents, 'Tenormin' prolongs atrial refractoriness
- Well tolerated by a wide variety of patients including those with life-threatening arrhythmias

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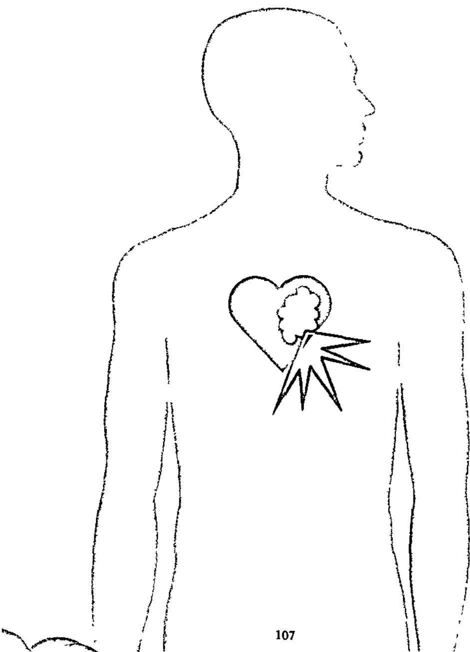
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2

'Tenormin' in acute myocardial infarction



Contents

'Tenormin' in acute myocardial infarction

Introduction

In treating patients who have coronary artery disease and who display signs of ischaemia, a major aim is to

'Tenormin' can prevent pre-infarct angina developing into an acute MI [2]

If a patient suffers an MI, short-term treatment with intravenous and oral 'Tenormin' early in the evolution of the infarct can reduce the extent of the infarction and save lives [3]

Those who survive an acute infarction are known to be at increased risk of dying suddenly or developing further

Why use a beta-blocker?

An infarction may arise from over-activation of the sympathetic nervous system which increases cardiac workload beyond the capacity of atheromatous coronary

sympathetic activity by a number of different

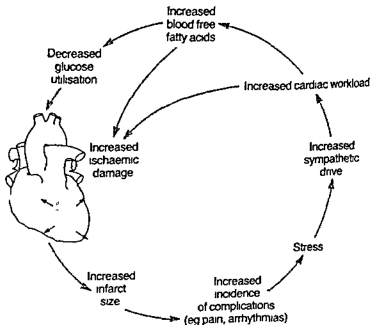
'Tenormin' treatment and the progression of pre-infarct angina to full infarction

Characteristics of pre-infarct angina

Pre-infarct angina – also known as crescendo, accelerated or progressive angina or threatened MI – may occur during exercise or at rest and may be easily [illegible]

It is characterised by severe pain lasting several hours and severe S-T segment elevation or depression Depending on the severity, there may also be a low level of cardiac-enzyme release into the circulation – an indication that a frank infarction is impending

Figure 1.
Representation of the possible vicious cycle involving metabolic consequences of sympathetic stimulation in connection with a myocardial infarction



Adapted from Opie LH, *et al* *Lancet* 1977, 2: 890-92

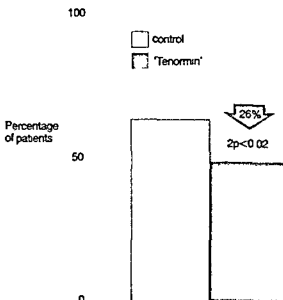
Risks to the patient

An estimated 45% of patients with acute MI have prodromal symptoms (eg chest pain)[1] In one series of [illegible]

treatment during the warning period may prevent progression to irreversible cardiac damage and save lives

'Tenormin' reduces the risk of developing full MI

[illegible]



[illegible]

mortality.[2] There was no indication that 'Tenormin' caused any irreversible effect on cardiac function [2] The results of this encouraging trial provided the basis for a large-scale study[3] designed to ...

Thus, patients at special risk may be afforded protection from a full MI by early short-term administration of 'Tenormin'

Calcium antagonists in patients with deteriorating pre-infarct angina

A controlled study examined the outcome of 105 ...

protect against progression of their pre-infarct angina to full infarction[39] (Figure 3)

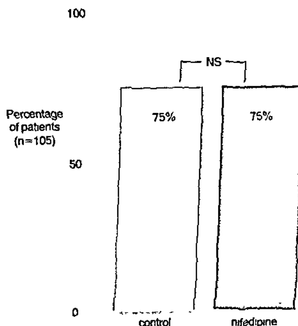


Figure 3.
No effect on progression of threatened to acute MI

sympathetic activity (with a consequent increase in heart

'Tenormin' in acute MI

Characteristics of myocardial infarction

Myocardial infarction usually occurs after several hours of pain and its severity depends on the degree of imbalance between oxygen supply and demand

interruption of the oxygen supply

Risks to the patient

of chest pain However, development can continue for

'Tenormin' saves lives

The International Study of Infarct Survival (ISIS), reported in 1986, demonstrated that short-term

ts

centres in 11 countries.

The patients were a low-risk group (individuals with hypotension or significant bradycardia were excluded)

Beta-blockade was maintained with oral 'Tenormin' (100 mg/day) for a further seven days.[3]

significant reduction in the number of

'Tenormin' treatment stopped after seven days

category of patients had a

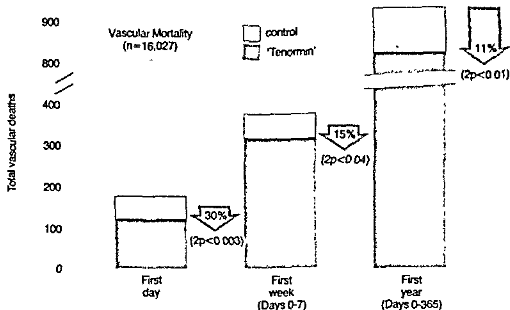


Figure 4.
The effect of early intervention with 'Tenormin' in reducing mortality in acute myocardial infarction

The benefits of 'Tenormin' in acute MI

'Tenormin' reduces infarct size

The results of ISIS suggested that early 'Tenormin' [illegible] mechanism by which short-term administration of intravenous 'Tenormin' protected against mortality was elucidated by the ISIS pilot trial[2] (see also earlier in this chapter).

The extent of myocardial damage was measured by cardiac-enzyme (creatine kinase isoenzyme – CK-MB) release and R-wave score on the ECG.[2] Both tests produced indirect measurements which, together, correlated well with infarct size.[5] Short-term intravenous and oral administration of 'Tenormin' in a group of 707 [illegible]

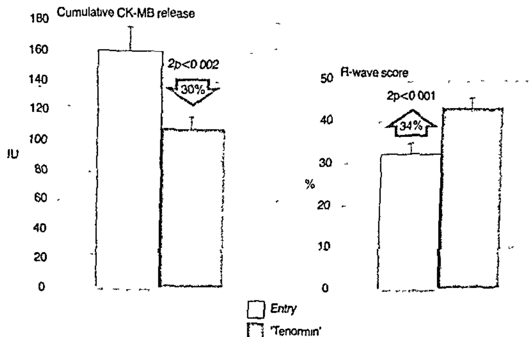


Figure 5.
Cumulative CK-MB release and R-wave scores in patients with initial definite MI

reduced after beta-blockade

Anti-arrhythmic action

monitored for ventricular premature complexes by 24-

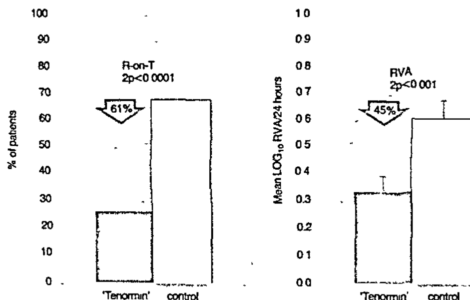


Figure 6.
Reduction in R-on-T ectopic complexes and repetitive ventricular arrhythmias (RVA) in the first 24 hours

Figure 7.
Reduced chest pain after 'Tenormin'

Objective Pain Score

Subjective Pain Score

Pain Score

Time (mins)

---saline
——'Tenormin'

* $p<0.05$
+ $p<0.01$

'Tenormin' relieves chest pain

Pain during infarction is probably related to ischaemia in the necrotic area which stimulates sensory neurones (Figure 1). The pain triggers a further release of catecholamines and beta-blockers such as 'Tenormin', which relieve pain, also decrease heart rate, blood pressure and ECG abnormalities [11,13,15]

One group demonstrated that the reduction in cardiac

ic

that, *"Beta-blockers must be given a more important place in the management of chest pain due to myocardial infarction"*[63]

A small number of other trials, including a large, multicentre, placebo-controlled trial, have also demonstrated a reduction in chest pain in patients with MI after they received other beta-blockers.[13-15]

Calcium antagonists and ACE inhibitors in MI

Calcium antagonists have not been shown to reduce infarct size or mortality in acute MI and, in man, may even increase mortality In a randomised study, 66 patients with acute MI received nifedipine or placebo about 4.5 hours after the onset of pain [39] There was no difference in cumulative CK-MB levels between the two groups, indicating that nifedipine did not influence the extent of infarction.

Several other studies, in which nifedipine was administered early in acute MI, confirmed this observation [64 67] Four studies showed that verapamil did not consistently reduce infarct size[68 69 70] or re-infarction rate.[69,71]

In the randomised study described above,[39] overall

of nifedipine and verapamil on mortality [64 65,72] As a result, it has been concluded that, "*Nifedipine did not affect the progression to acute infarction among the patients with threatened infarction nor did it alter infarct size There was, in fact, a tendency to a higher mortality in the nifedipine-treated patients* "[73]

There is also no convincing evidence that

inhibitors

Continued beta-blockade protects against re-infarction

Risks to the patient

Survivors of an acute infarction are at increased risk of

37% if unstable angina develops.[1]

Angina developing post-infarct may also increase the risk of mortality.[78-80] During the first post-infarction year, there is a 10% mortality and in the subsequent 2-3 years, a 4% annual mortality.[81] About half of the post-hospital deaths are sudden (more than twice as common as non-sudden deaths[4]) and are mainly due to ventricular fibrillation.[77]

One-year mortality increases exponentially after the age [illegible]

probable MI [illegible]

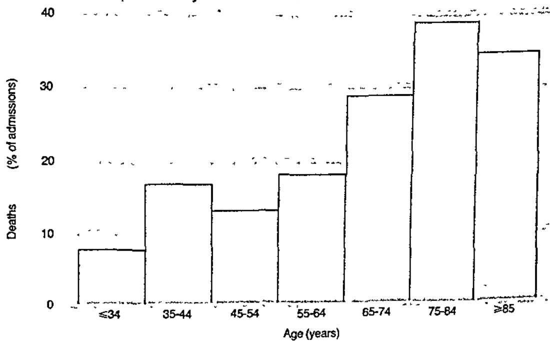


Figure 8.
The effect of age on in-hospital mortality from a definite or probable myocardial infarction

Other factors increasing the likelihood of post-infarct [illegible]

[illegible] were

public health terms[5] and should be distinguished from treatments which confer no material benefit. *"Typically, treatment [with beta-blockade] of about 200 patients for one year . . might be expected to avoid about 3 deaths and about 3 non-fatal reinfarctions."*[3]

'Tenormin' – an effective treatment in post-infarct angina

As described in the 'Angina' chapter, 'Tenormin' is highly [illegible]

effective than diltiazem or nifedipine.[86,87] Therefore, 'Tenormin' can protect against the recurrence of angina in post-infarct patients.

Long-term benefit with beta-blockade

Pooling the results from long-term randomised studies yielded an extensive patient base of over 23,500. Analysis of the pooled mortality data demonstrated that [illegible]

patients who were randomised to 'Tenormin' during the first week of treatment (11%, 2p<0.01) compared with [illegible]

[illegible]

beta-blocker after an infarction.

[illegible]

[illegible]

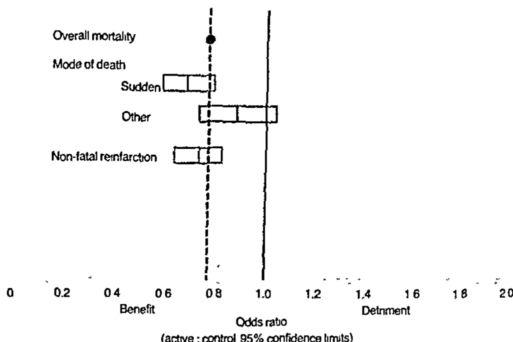


Figure 9.
Mode of death in long-term β-blocker trials post MI[3,5]

Which patients benefit most from beta-blockade?

In some studies, attempts have been made to identify categories of patients most likely to benefit from a

Beta-blocker benefit due to sympathetic blockade

The protective effect of beta-blockers on the myocardium was mainly due to blockade of β_1-receptors *per se* as both cardioselective and non-selective blockers were effective.[5] There was no indication that membrane

There was a *strong correlation* between a reduction in

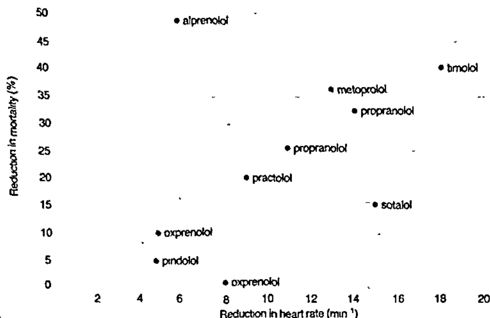


Figure 10.
Relationship between reduction in heart rate and reduction in mortality.

almost linear relationship between the reduction in resting rate and mortality. The larger the reduction in heart rate, the larger is the reduction in

[illegible]

Long-term benefit from calcium antagonists

In long-term studies with nifedipine and verapamil there [illegible]

calcium antagonists, there is no convincing evidence for secondary prevention."[97]

Nifedipine

The Secondary Prevention of Re-Infarction Nifedipine Trial (SPRINT) included 2279 survivors of an infarction [illegible]

months of treatment, nifedipine did not significantly reduce mortality or non-fatal re-infarction.[97]

As mentioned earlier in this chapter, unlike 'Tenormin', nifedipine does not decrease heart rate and may even increase it.[40] A reflex increase in heart rate could, in certain cases, outweigh the benefit of a reduction in coronary artery tone.

Verapamil

A total of 1436 patients admitted to coronary care units [illegible]

Summary: 'Tenormin' in acute myocardial infarction

- There is strong evidence that over-activation of the sympathetic nervous system is an important contributor to the development of an infarction
- Beta-blockade with 'Tenormin' offers protection against the consequences of excessive sympathetic discharge
- 'Tenormin' protects pre-infarct patients from developing a full MI
- 'Tenormin' saves lives in acute MI
- 'Tenormin' protects the heart at risk by reducing infarct size and reducing the incidence of arrhythmias
- [illegible]

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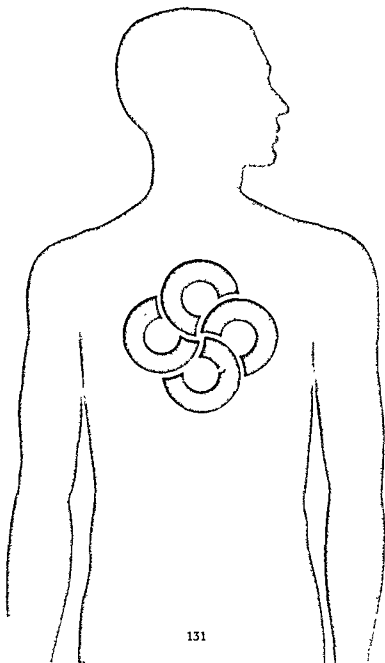
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Drug interactions with 'Tenormin'



Contents
Drug interactions with 'Tenormin'

combined medication.

proportion of the parent compound needs to be metabolised before changes in blood levels and potential clinical symptoms become evident.

Table 1. Some factors affecting drug pharmacokinetics.

Common factors affecting drug pharmacokinetics	Pharmacokinetic parameter influenced: Absorption	Distribution	Metabolism	Excretion
Water/lipid solubility	○	○	○	○
Blood flow:				
gastrointestinal tract	○			
cardiac output		○		
liver			○	
kidney				○
Competition for:				
absorbing site	○			
protein binding site		○		
metabolising site			○	
tubule secreting site				○
Organ function	○		○	○
Other factors:				
Physicochemical properties of drug	○			
Enzyme induction			○	
Enzyme inhibition			○	

enzymes of the cytochrome P_{450} system Plasma levels of drug and/or metabolite may be affected if two drugs

The second type – pharmacodynamic interactions – are generally more predictable provided the pharmacology of the drugs is known and may include haemodynamic and electrophysiological mechanisms. Hepatic drug metabolism is also dependent on hepatic blood flow which, if altered, may affect plasma drug levels by changing the rate of drug presentation to the metabolising enzymes.

Lipid solubility – an important determinant of pharmacokinetic interactions

Whilst the cardioselectivity of beta-blockers does not appear to be an important factor in determining drug interactions, lipid solubility is of characteristic importance. The water/lipid solubility of a beta-blocker ... and distribution but also

It is found in practice to be relatively insensitive to

blocker

Which drugs interact with 'Tenormin'?

The results of trials designed to investigate the drugs with

Calcium antagonists

... often be prescribed with

Table 2. Effect of co-prescribed drugs on 'Tenormin'.

Drug	Effect on 'Tenormin'	Relevant clinical effects	Referenc
Acetylsalicylic acid	None	None	31
Alcohol	None	None	55,56
Allopurinol	None	None	31
Aluminium hydroxide	Decreased bioavailability	None	8,50
Amitriptyline	None	None	54
Ampicillin	Decreased bioavailability	Unknown	31,59
Calcium	Decreased bioavailability	None	8
Chlorthalidone	None	Enhanced b p. reduction	6,7
Cimetidine	None	None	38,40,65
Diazepam	None	None	52
Flurbiprofen	None	None	36
Food	Decreased bioavailability	None	62
Frusemide	None	None	8
Hydralazine	None	None	9
Indomethacin	Unknown	Increase in b p.	32
Isosorbide dinitrate	None	None	12
Metoclopramide	None	None	50
Nifedipine	None	Enhanced b p. reduction	2,66
Propantheline	Increased bioavailability	None	50
Ranitidine	None	None	38,45
Smoking	None	None	3
Sulindac	Unknown	None	32

b p. = blood pressure

Nifedipine

As it is also relevant to know if the two types of agent interact pharmacokinetically, the disposition of 'Tenormin', metoprolol and propranolol were each

Table 3. Effect of 'Tenormin' on other drugs.

Drug	Effect of 'Tenormin' on other drug	Relevant clinical effects	Referenc
Acenocoumarin	Unknown	None	18
Alcohol	*None*	None	55,56
Antipyrine	None	*None*	*30*
Disopyramide	Decreased clearance	Unknown	*28*
7-Ethoxycoumarin	None	*None*	*13*
Isosorbide dinitrate	None	None	12
Lignocaine	None	*None*	*20*
Phenprocoumon	None	None	*17*
Tolbutamide	None	*None*	*20*
Verapamil	None	*None*	*4*
Warfarin	Increased peak blood levels	None	14

Verapamil

[illegible] rly in patients with impaired ventricular function, and this combination should not be given to patients with conduction abnormalities (see Prescribing Information).

[illegible] increased propranolol [illegible]

Diuretics – complementary action particularly useful in hypertension

Chlorthalidone

The antihypertensive effect of fixed combinations of 'Tenormin' with chlorthalidone ('Tenoretic' and 'Tenoret' [illegible] equivalent to the free [illegible]

[illegible] pharmacokinetic interaction [illegible] ' in hypertensive [illegible]

Frusemide

Frusemide has no effect on the bioavailability of 'Tenormin'.[8]

Vasodilators – no effect on 'Tenormin' kinetics

Hydralazine

The pharmacokinetics of 100mg 'Tenormin' were unaffected by concurrent oral administration of 25 or [illegible] changes rather than a metabolic interaction [11]

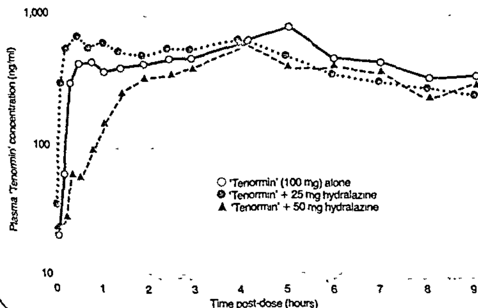


Figure 1.
Effect of oral administration of hydralazine on plasma concentrations of 'Tenormin'

Isosorbide dinitrate

Neither 'Tenormin' nor isosorbide dinitrate had any effect on the pharmacokinetics of each other.[12]

Anticoagulant status unaffected by 'Tenormin'

A further potentially important source of drug interactions is the co-administration of beta-blockers with anticoagulants, eg in patients with myocardial infarction. 'Tenormin' does not display any adverse clinical sequelae when administered with anticoagulants.

7-Ethoxycoumarin

Using *in vitro* preparations of hepatic microsomal enzymes, 'Tenormin', unlike propranolol, did not inhibit 7-ethoxycoumarin metabolism[13] (Figure 2). The

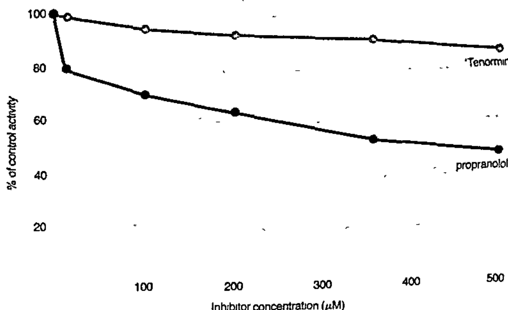


Figure 2.
Effect of propranolol and 'Tenormin' on 7-ethoxycoumarin deethylase activity

Warfarin

[illegible]

warfarin [illegible]

Phenprocoumon

[illegible]

on phenprocoumon, the investigators related, *"Although the transient increase of phenprocoumon plasma levels caused by metoprolol may be of little clinical significance after a single dose of phenprocoumon, a more important alteration in phenprocoumon disposition and effect should be* [illegible]

therapy."[17]

Acenocoumarin

The activity of acenocoumarin, in patients receiving this [illegible]

Anti-arrhythmic agents – more evidence required

Lignocaine

[illegible]

(Figure 3)

As a result of the low therapeutic index of lignocaine, it may exhibit toxicity if plasma levels increase above normal This is particularly relevant to post-infarction patients

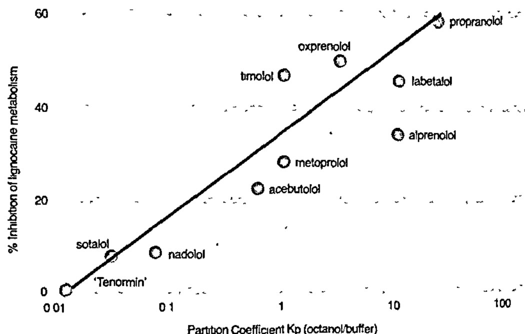


Figure 3.
Relationship between % inhibition of lignocaine metabolism by rat liver microsomes for different β-blockers[19]

Disopyramide

are conflicting.[24 27]

Anti-inflammatory and analgesic agents – a possible interaction with beta-blockers?

Antipyrine

Preliminary work indicated that there was no difference [illegible] standard once-daily dose of 100mg 'Tenormin' had no effect on the clearance, volume of distribution and elimination half-life of antipyrine in normal volunteers [30] [illegible] significantly lowered the mean plasma clearance of antipyrine at equal degrees of beta-blockade

Acetylsalicylic acid

In healthy volunteers, 500mg acetylsalicylic acid did not alter the pharmacokinetics of 'Tenormin'.[31]

Indomethacin, sulindac

Indomethacin appears to increase blood pressure in hypertensive patients treated with different beta-blockers including 'Tenormin', oxprenolol, pindolol and propranolol,[32-35] but this property is not shared with the anti-inflammatory agent, sulindac [32] The speculated pharmacodynamic mechanism may involve opposing effects on systemic and/or renal prostaglandins [32]

Flurbiprofen

[illegible]

Histamine (H_2)-receptor blockers – concurrent use with certain lipophilic beta-blockers may cause problems

[illegible] solution to the problem as it has not been shown to interact with this class of drug

Cimetidine

probably by inhibition of the drug metab

'Tenormin' was not affected by co-administration of

[40]

as

by biotransformation,[38] or penbutolol, which is mainly eliminated by phase II reactions such as glucuronidation.[38]

Cimetidine pharmacokinetics were unaffected by beta-blocker administration [38]

Table 4. Beta-blocker/cimetidine interactions[38]
(Drugs administered for 7 days to 6 patients)

Treatment		Peak plasma conc (ng ml^{-1})	AUC (ng ml^{-1}h)	Elimination half-life (h)
Metoprolol 100 mg bid	Alone	177	1,167	4 4
	Plus cimetidine	284*	1,885*	7 0
Propranolol 80 mg bid	Alone	126	948	5 6
	Plus cimetidine	251*	2,112*	7 6
'Tenormin' 100 mg daily	Alone	660	5,787	7 4
	Plus *cimetidine*	610	5,827	7 5

* = $p < 0 05$

No pharmacodynamic interaction was reported in

Ranitidine

[illegible] clarification.

Other anti-ulcer drugs – no clinically important interaction with 'Tenormin'

[illegible]

Aluminium hydroxide

Aluminium hydroxide reduced the bioavailability of [illegible] an increase in gastric pH affecting the dissolution rate of 'Tenormin'[50]

Propantheline

[illegible] is unlikely to affect the degree of beta-blockade by 'Tenormin' in view of its flat dose-response curve.

Metoclopramide

Metoclopramide increases the rate of gastric emptying but has no effect on the bioavailability of 'Tenormin'[50]

Psychotropic drugs – no interaction with 'Tenormin'

Diazepam

[illegible] propranolol, but not by 'Tenormin'.[51,52] The increased plasma levels of diazepam and metabolites produced by the lipophilic beta-blockers were closely associated with an impairment of psychomotor performance.[52]

'Tenormin' did not impair subjects' psychomotor function even when administered with diazepam. Hawksworth and colleagues noted that when diazepam needs to be given with a beta-blocker, "*... use of a hydrophilic β-adrenoceptor antagonist would appear to minimise the incidence of adverse side effects.*"[52]

Other aspects of the psychomotor testing carried out in this study are described in the 'Hydrophilicity' chapter

Amitriptyline

In healthy subjects who received 'Tenormin' or metoprolol in combination with amitriptyline, there was

The pharmacokinetics of 'Tenormin' were not altered by amitriptyline.

Alcohol

Alcohol ingestion activated propranolol metabolism,[56]

The pharmacokinetics of 'Tenormin' were unchanged by alcohol ingestion and *vice versa.*[55,56]

Smoking has less effect on 'Tenormin' than on lipophilic beta-blockers

Cigarette smoking

In addition to increasing heart rate and blood pressure,[57] cigarette smoking may also induce liver drug

s less

of propranolol and nifedipine were lower in patients on smoking than in patients off smoking but the differences

study[58]

Table 5. Area and severity of S-T segment depression measured immediately after exercise[3]

		Smoking	*No Smoking*
Placebo	area	5 6 ± 3.2	4 1 ± 3.2
	severity	6 8 ± 4 0	5 4 ± 3 4
'Tenormin'	area	2 0 ± 1 8	1.4 ± 1 4
	severity	2 5 ± 2 6	1.7 ± 1 7
Propranolol	area	2.6 ± 2.0	1.9 ± 2.0
	severity	3 4 ± 2.7	2 5 ± 3.2
Nifedipine	area	3.9 ± 3.0	2.1 ± 2 8
	severity	5.3 ± 2.8	2.5 ± 3.3

Miscellaneous agents

Ampicillin

antibiotics are known to impair drug absorption,[60,61] the

'Tenormin' was unchanged in hypertensive patients receiving the same drug combination.[31]

Food

Under normal conditions, 'Tenormin' is only about 50% absorbed due to its hydrophilic nature (see 'Pharmacokinetics' chapter) Ingestion of food reduced the absorption of 'Tenormin' by approximately 20% but this was not thought to have any clinically relevant consequences.[62]

In direct contrast, the bioavailability of metoprolol and propranolol were enhanced by food intake probably due [illegible]

Calcium

[illegible]

normal subjects experienced a reduction in exercise tachycardia Nevertheless, blood pressure control was unimpaired in hypertensive patients receiving the same combination.[8]

Allopurinol

In healthy volunteers, allopurinol had no demonstrable effect on the pharmacokinetics of 'Tenormin'[31]

Tolbutamide

The bioavailability and clearance of tolbutamide in normal volunteers was unaffected by 'Tenormin'[20]

Summary: Drug interactions with 'Tenormin'

- Consistent pharmacokinetics enable prediction of possible drug interactions
- Beneficial pharmacodynamic interactions with diuretics and some calcium antagonists confer important therapeutic advantages for patients
- Hydrophilic molecule means few liver-mediated drug interactions
- Unlike lipophilic beta-blockers, 'Tenormin' kinetics are unaffected by cimetidine and hydralazine
- Less affected by enzyme inducer, nicotine, than lipophilic beta-blockers
- Bioavailability altered only by a small number of agents usually without adverse clinical sequelae
- Caution may be necessary if patients are also taking verapamil or disopyramide

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and propranolol
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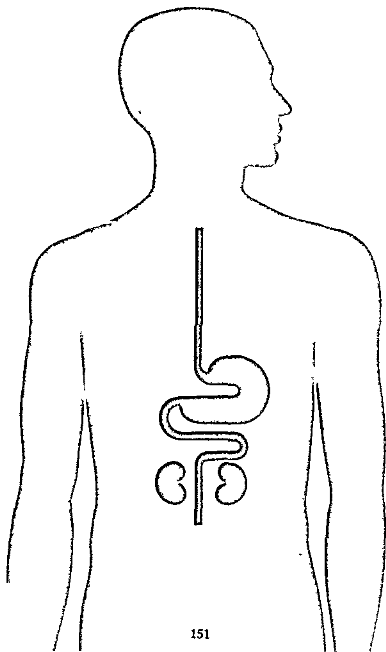
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'Tenormin' pharmacokinetics



Contents 'Tenormin' pharmacokinetics

Consistent bioavailability = predictable clinical response

Patients with normal renal and hepatic function

Bioavailability of 'Tenormin' is reflected in the blood levels of the drug as well as its accumulation in the urine and is a consequence of its minimal metabolism (<10%)[1] and low biliary excretion [2] Approximately 50% of 'Tenormin' is absorbed after oral administration[3-6] and urinary recovery of 'Tenormin' is of the order of 95% (after iv administration)[3] and 50% (oral administration) respectively[3] (see summary in Table 1)

Ingestion of food reduces the mean area-under-the-curve (AUC) values by 20% after acute administration of 'Tenormin'[7] but is unlikely to have any clinical consequences in view of the flat 'Tenormin' dose-response curve (see 'Hypertension' chapter)

Peak plasma levels are reached approximately 2-4 hours after repeated oral dosing (100mg/day) and do not differ

of its negligible liver metabolism [5] Consequently, consistent blood levels are achieved with a predictable clinical response.

Simple kinetic profile gives few clinical problems

'Tenormin' is only 3% protein bound in the plasma[8] and

The elimination half-life of 'Tenormin' following chronic oral administration to patients with normal renal function is 6-9 hours[3 5 6,10] and is of the same order as

Table 1. 'Tenormin' – summary of pharmacokinetic data[3,5,13,30]

	Dose (mg)	$t_{1/2}$ (hours)	Bioavailability (%)	Mean C_{max} (ng/ml)	Mean T_{max} (minutes)	Mean $AUC_{0-\infty}$ (ng ml^{-1} h)	Mean Vol distribution (L/kg)
Oral	100	6-9	50	600	2-4	6000	–
Intravenous	50	6-9	95	–	–	4730	0 7

Patients with impaired renal function

Clinically-verified dose recommendations

values 13 14 Similar results were obtained after single

Dose recommendations have been calculated in order to avoid excessive blood levels of 'Tenormin'[13] and have been verified in patients with impaired renal function[15] (for further details see Prescribing Information)

'Tenormin' – elimination by haemodialysis

'Tenormin' is readily dialysable due to very lc

of 50% for each dialysis.[17]

In the dialysis interval, 'Tenormin' is eliminat

Minimal problems with impaired liver function

generally unaffected by alterations in liver function [18-20] Nevertheless, in a small number of patients with chronic liver disease, transient changes in renal function may occur, leading to delayed excretion of 'Tenormin' [20]

Kinetics unaffected by thyroid disease

'Tenormin' and elderly patients

Renal and hepatic function decrease with age[22,23] and therefore a lipophilic beta-blocker such as metoprolol, which is metabolised, shows marked variations in peak plasma levels in young and elderly subjects [24] However, 'Tenormin' is virtually unmetabolised and does not accumulate significantly at glomerular filtration rates above 35ml/min.[13]

The kinetics of 'Tenormin' have been compared in young and elderly (66-78 year old) male subjects given single oral (100mg) or intravenous (10mg) doses. There was no significant effect of increasing age on clearance, volume of distribution or bioavailability of 'Tenormin'[25] The

In contrast, the results of a second study provided a different view Barber and colleagues calculated

Table 1. 'Tenormin' – summary of pharmacokinetic data[3,5,13,30]

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Intravenous	50	6-9	95	–	–	4730	0 7

Clinically-verified dose recommendations

Patients with impaired renal function

The peak and 24-hour plasma concentrations of 'Tenormin' increase as creatinine clearance decreases, as demonstrated by an increase in blood half-life and AUC values[13,14] ...

Dose recommendations have been calculated in order to avoid excessive blood levels of 'Tenormin'[13] and have been verified in patients with impaired renal function[15] (for further details see Prescribing Information).

'Tenormin' – elimination by haemodialysis

'Tenormin' is readily dialysable due to very low protein ...

In the dialysis interval, 'Tenormin' is eliminated slowly[17] ...

... ven

Information section)

Minimal problems with impaired liver function

Unlike the lipophilic beta-blockers, propranolol, metoprolol, etc., 'Tenormin' undergoes only minimal hepatic metabolism and its elimination from the body is generally unaffected by alterations in liver function [18,20]. Nevertheless, in a small number of patients with chronic liver disease, transient changes in renal function may occur, leading to delayed excretion of 'Tenormin' [20].

Kinetics unaffected by thyroid disease

In contrast to metoprolol and propranolol, dosage adjustment of 'Tenormin' is unnecessary in patients with thyrotoxicosis as bioavailability is unaffected.[21]

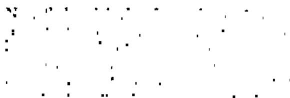
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[illegible]

In contrast, the results of a second study provided a different view. Barber and colleagues calculated [illegible]

[illegible] dose may be more appropriate for the elderly and yet still maintain optimal cardioselectivity



to a non-metabolised, cardioselective beta-blocker ['Tenormin'] . . .'[29]

Summary: 'Tenormin' pharmacokinetics

- ○ Simple kinetics due to hydrophilic molecule
- ○ Predictable clinical response to a fixed dose
- ○ Low volume of distribution contributes to low CNS penetration with low incidence of side-effects
- ○ Kinetics unaffected by thyroid or liver disease
- ○ Clinically-verified dose recommendations for patients with impaired renal function
- ○ Minimal effect of age on kinetics

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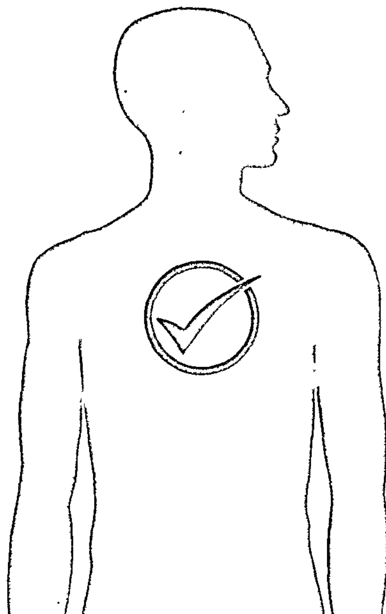
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Tolerability of 'Tenormin'



Contents
Tolerability of 'Tenormin'

Adverse reaction reporting systems

[illegible]

extremely low

In general, the reporting of the incidence of side-effects varies enormously with the evaluation technique employed. It is recognised that the incidence of "events" (synonymous with adverse reactions or side-effects) is [illegible] inability to establish a causal link between drug and "events"[1]

One of the most reliable methods is that based on a double-blind, placebo-controlled trial where the placebo effects can be subtracted from the effects of the active drug Several of these studies as well as large-scale patient surveys have been used to assess the tolerability profile of 'Tenormin'. Some of the adverse reactions have been classified into those which can be predicted from the pharmacological properties of the molecule and those which are idiosyncratic.

Most studies show only minor side-effects with 'Tenormin'

Double-blind trials

In 11 separate double-blind, randomised trials, side-effects were assessed in 482 patients with mild to moderate hypertension Their ages ranged from 18-65 years and they received 'Tenormin' (100-300mg daily) or placebo for at least one month before answering questions from a symptom check list[2]

Cold extremities and fatigue were seen more often with 'Tenormin' and their incidence accounted almost exclusively for the higher total incidence of side-effects in the 'Tenormin'-treated group (Table 1)

Table 1: Adverse effects of 'Tenormin' and placebo (n=482).

	Placebo		'Tenormin'	
Side-effects	**n**	**%**	**n**	**%**
Cold extremities	47	9.8	75	15.6
Fatigue	82	17.0	107	22.2
Bronchospasm	27	5.6	30	6.2
Indigestion	16	3.3	16	3.3
Diarrhoea	2	0.4	7	1.5
Constipation	24	5.0	13	2.7
Vivid dreams	17	3.5	14	2.9
Insomnia	12	2.5	9	1.9
Dizziness	31	6.4	37	7.7
Depression	30	6.2	26	5.4
Impotence	12	2.5	13	2.7
Paraesthesia	10	2.1	13	2.7
Skin rash	4	0.8	3	0.6
Ataxia	1	0.2	3	0.6
Total	315		366	

Other physicians have similarly noted that the "true"

95% of patients report feelings of well-being

... study was conducted

of the group.[6]

A subjective feeling of well-being was reported by 95% of

Table 2. Twenty most frequently reported side-effects based on 39,745 patients.

Adverse effect	Number reported	Percent
Headache	628	1.6
Dizziness	628	1.6
Tiredness	497	1.3
Nausea	461	1.2
Fatigue	439	1 1
Weakness	375	0 9
Lightheadedness	268	0.7
Bradycardia	232	0 6
Oedema	216	0 5
Diarrhoea	203	0 5
Depression	184	0 5
Impotence	149	0.4
Dyspnoea	144	0 4
Nervousness	141	0 4
Chest pain	126	0 3
Lethargy	117	0 3
Malaise	115	0.3
Dry mouth	111	0.3
Drowsiness	108	0.3
Increased blood pressure	105	0 3

[illegible]

Long-term tolerability

[illegible]

[illegible]

because of side-effects, the most common reason being

Table 1: Adverse effects of 'Tenormin' and placebo (n=482).

	Placebo		'Tenormin'	
Side-effects	n	%	n	%
Cold extremities	47	9 8	75	15 6
Fatigue	82	17 0	107	22 2
Bronchospasm	27	5 6	30	6 2
Indigestion	16	3.3	16	3 3
Diarrhoea	2	0 4	7	1.5
Constipation	24	5.0	13	2 7
Vivid dreams	17	3.5	14	2 9
Insomnia	12	2 5	9	1.9
Dizziness	31	6 4	37	7 7
Depression	30	6.2	26	5.4
Impotence	12	2.5	13	2 7
Paraesthesia	10	2 1	13	2.7
Skin rash	4	0 8	3	0 6
Ataxia	1	0.2	3	0 6
Total	315		366	

Other physicians have similarly noted that the "true" side-effects of 'Tenormin', reported by patients, were muscle fatigue and cold extremities [3] The overall number of side-effects to 'Tenormin' treatment was equally low in other double-blind studies [4,5]

95% of patients report feelings of well-being

A large postmarketing surveillance study was conducted in a predominantly middle-aged to elderly population of 39,745 hypertensive patients, 34,120 of whom completed 28 days' treatment with 'Tenormin'. These patients were treated for one month with 50mg 'Tenormin' daily, which produced satisfactory blood pressure control in 71-80% of the group.[6]

A subjective feeling of well-being was reported by 95% of

... by physicians. The twenty most reported side-

[illegible]
reason for stopping or changing 'Tenormin' treatment. Further evidence is provided by Simpson who had to withdraw only one patient out of a group of 543 because of symptomatic bradycardia.[18]

[illegible]
the frequency of dizziness, fatigue and cold extremities was similar in all age groups, indicating that the elderly were not likely to experience any extra problems. Additionally, in a subgroup of 482 patients who received 'Tenormin' for at least one month, the reported frequency of dizziness was similar to placebo (Table 1).[2]

Minimal incidence of heart failure

Heart failure has rarely been reported with 'Tenormin'.[8,19] Furthermore, in patients with myocardial infarction, a reduction in the incidence of heart failure, from 24% in controls to 19%, was recorded after acute intervention with 'Tenormin'.[17] A second study involving myocardial infarction patients also recorded a lower incidence of heart failure after 'Tenormin' compared with placebo or propranolol treatment.[20]

This beneficial action of 'Tenormin' may be due to a reduction in infarct size and consequently preservation of a viable myocardium

No requirement for additional inotropic agents

[illegible]
infarction.[21]

The advantages of cardioselectivity

The advantages of cardioselective 'Tenormin' for a wide variety of patients and, in particular, for the asthmatic and diabetic patient, have already been described in the 'Cardioselectivity' chapter.

Low risk of cold extremities

Whilst reports of cold extremities are common to all
[illegible]
survey of patients who completed self-assessment questionnaires showed that cold digits were perceived

indigestion (n=3). "Prohibitive" side-effects such as bronchospasm occurred much less frequently with

and propranolol-treated patients (14.4%) as did the minor "tolerable" side-effects [8]

A further large open study has confirmed the good tolerability of 'Tenormin'.[10]

Comparison with other antihypertensive drugs

A number of studies have attempted to define the overall

in routine use.

The total incidence of side-effects was generally similar

With methyldopa, "*... most patients do not realize that they have been suffering from tiredness or drowsiness until they change to another drug regime*"[12]

Incidence of side-effects is not related to pharmacological profile

Influence of heart rate

Slowing of the heart rate is a consequence of the

The benefits of hydrophilicity by substituting 'Tenormin' in place of lipophilic beta-blockers

The hydrophilic nature of 'Tenormin' is reflected in a very low frequency of CNS side-effects. The other major benefits of hydrophilicity are discussed in more depth in the 'Hydrophilicity' chapter.

In various trials, including double-blind and randomised studies, the use of lipophilic beta-blockers has been [illegible] abolished.

[illegible] drug.[37,39-43] Reports of sleep disturbances, insomnia and restless nights were all significantly lower with 'Tenormin' than pindolol or metoprolol.[37,39,41]

Patients who received 'Tenormin' as a substitute medication reported a significant preference ($p<0.05$) for 'Tenormin' over metoprolol and propranolol[40] and had fewer CNS problems such as nightmares, hallucinations[40] and visual perceptual disorders.[42] One investigator concluded, *"CNS side effects on β-blockers . can be very unpleasant for the individual* [illegible]

[illegible] 'Tenormin' in view of its hydrophilic properties.[43] The patient response to this change in medication was monitored over 1-4 years and is summarised in Table 3. The investigators concluded, *"['Tenormin'] seems to give much less problems [with] the CNS and this impression has been maintained during more than 1000 patient-years."*[43]

least often with 'Tenormin' compared with other beta-blockers including non-selective agents, the incidence being similar to placebo.[23]

Low risk of fatigue

performance than non-selective beta-blockers. Overall, beta-blockers did not inhibit the response to physical training,[24] however, non-selective agents such as propranolol and pindolol caused more impairment of physical performance (maximum exercise load and exercise duration)[25-28] than 'Tenormin' and this was particularly noticeable in subjects with a high percentage of slow-twitch muscle fibres.[25] 'Tenormin' also

In one other study, fatigue developed early in treatment with 'Tenormin' but resolved spontaneously after 2–3 weeks or with a reduction in dosage.[32]

Lipoproteins

be more relevant.[33]

Glucose tolerance

Non-pharmacological (idiosyncratic) side-effects of 'Tenormin' are rare

[illegible]

placebo or not at all [2,18] However, isolated case reports of skin rashes due to beta-blockers including 'Tenormin' have been published [49 51]

Gastrointestinal symptoms such as diarrhoea, constipation and indigestion all occurred at placebo level as did impotence and depression (Table 1) [2]

The oculomucocutaneous syndrome, described for practolol, has not been reported with 'Tenormin' and in 14 patients who developed the syndrome on practolol, all improved on switching to 'Tenormin'.[8]

Laboratory values

[illegible]

SGOT, SGPT, bilirubin, alkaline phosphatase, serum urate and creatinine or urinary glucose and protein [4]

[illegible]

The elderly do not experience more side-effects with 'Tenormin' than younger patients

Effect of age on side-effects

In the large patient survey described earlier in this chapter, the elderly experienced no more side-effects than younger patients[2] and this was confirmed by a further study in the elderly.[52]

A controlled trial is currently underway to test the [illegible]

group, completed self-administered questionnaires

Table 3. Patient response to medication changeover (lipophilic beta-blocker to 'Tenormin').

Symptoms	Number of reports	Symptom disappeared or clearly improved (%)
Nightmares, insomnia and/or hallucinations	55	91
Fatigue and/or depression	42	60
Gastrointestinal trouble	26	85
Bronchospasm	16	94
Impotence	6	33
Cold hands	6	50

Other subjective and objective effects of various beta- [illegible] 15mg/day).

'Tenormin' was indistinguishable from placebo and produced significantly fewer reports of dreams than [illegible] waking than pindolol and propranolol (p=0.01). A disturbance of the sleep EEG was noted with pindolol.

[illegible]

Further supportive evidence has been published in [illegible] of 'Tenormin' in place of [illegible] once 'Tenormin' was substituted for their previous beta-blocker medication.

However, in order to minimise risk it is recommended that, in patients with ischaemic heart disease, withdrawal of 'Tenormin' should be gradual (see Prescribing Information section)

Few problems with 'Tenormin' even in overdose

Tolerability in overdose

Beta-blockers are agents with a high benefit-to-risk ratio and very large doses are usually well tolerated The clinical outcome of beta-blocker overdose can be [illegible] unless other drugs or alcohol had also been consumed.[57]

One case has been reported of a patient who ingested [illegible] uncomplicated [58]

One of the highest known overdoses with 'Tenormin' [illegible] 100mg [illegible] combination of digoxin, verapamil and a morphine derivative.[59] He was admitted 1½ hours later and [illegible] incomplete right-sided block and grade I AV block There were no signs of heart failure.

After treatment, he made a full recovery and no 'Tenormin' was detectable in his serum four days after the overdose.[59]

Summary: Tolerability of 'Tenormin'

- Tolerability profile confirmed in large patient studies
- Less than 3% withdrawal rate due to drug intolerance
- Similar incidence of side-effects to placebo except for the well-documented beta-blocker side-effects of fatigue and cold extremities
- Hydrophilic and cardioselective properties confer important benefits in the form of a low incidence of side-effects
- No changes in hepatic or renal function
- No changes in laboratory values
- Little evidence of withdrawal phenomena although caution is recommended
- Well-tolerated even in overdose

Preliminary analysis of questionnaires showed that the treated group had a similar level of complaints to the untreated and control groups (Table 4).[53]

Table 4. Side-effects in elderly hypertensive patients.

Incidence (%) in each group

Side-effect	Normotensive patients*	Hypertensive controls	Hypertensive treated
Headache	17	19	19
Tiredness	63	51	58
Breathlessness	55	37	51
Vertigo	38	23	26
Depression	13	17	14
Indigestion	35	29	29
"Worries"	44	30	30
Generally unwell	32	24	35

*1 in 5 sample

Little evidence for involvement of 'Tenormin' in beta-blocker withdrawal syndrome

Controversy surrounds the exact nature of the "beta-blocker withdrawal syndrome" and whether it is a real phenomenon. The conflicting evidence has included anecdotal reports as well as controlled studies and the "syndrome" generally occurred in patients receiving propranolol [54]

The effects of abrupt withdrawal of 'Tenormin' treatment have recently been examined in a group of 20 patients

these subjects and it was concluded, "... *the clinical consequences of abrupt ['Tenormin'] withdrawal are usually minor and predictable corresponding with a gradual disappearance of beta-blockade over several days*"[55]

sensitivity

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daily or 100 mg once every two days For patients, with a creatinine clerance of < 15 ml/min/1.73 m² (equivalent to serum creatinine of > 600 micromol/litre) the oral dose should be 50 mg on alternate days or 100 mg once every four days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur

Pregnancy
'Tenormin' has been used effectively under close supervision for the treatment of pregnancy-associated hypertension There was no evidence of any foetal abnormalities although 'Tenormin' was generally given after 20 weeks gestation

'Tenormin' crosses the placental barrier and appears in cord blood. There is an approximate three-fold accumulation of 'Tenormin' in the breast milk However, there were no apparent detrimental effects in the baby at birth or during breast feeding

The possibility of foetal injury cannot be excluded and the use of the drug in women who are, or may become pregnant or who are nursing the newborn infant, requires that anticipated benefits be weighed against possible risks

SIDE EFFECTS
In clinical studies, the side effects reported are usually attributable to its pharmacological actions and include coldness of the extremities, muscular fatigue and, in isolated cases, bradycardia Sleep disturbances of the type noted with other beta-adrenoceptor blocking drugs have rarely been reported

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

OVER DOSAGE
From first principles, excessive bradycardia may be [illegible]

injection Care must be taken to ensure that the blood pressure does not fall too low if the dose of the beta-receptor agonist has to be increased

Glucagon has also been reported to be useful as a cardiac stimulant in a dose of 10 mg intravenously

PRESENTATION
'Tenormin' tablets each containing atenolol 100 mg and 50 mg

®Trademarks

TENORMIN® – Prescribing Information

USES

i) Control of hypertension [illegible]

[illegible]

'Tenormin' is *effective for at least 24 hours after a* single oral dose This facilitates compliance by its [illegible]

[illegible]

DOSAGE AND ADMINISTRATION

Adults

Hypertension:

Most patients respond to 50-100 mg daily given orally as a single dose The effect will be fully established after one to two weeks A further reduction in blood pressure may be achieved by combining 'Tenormin' with other antihypertensive agents For example, co-administration of 'Tenormin' with a diuretic provides a highly effective and convenient antihypertensive therapy

Angina:

Most patients with angina pectoris will respond to 100 mg daily given orally as a single or divided dose. It is unlikely that additional benefit will be *gained by increasing the dose*

Children

There is no paediatric experience with 'Tenormin' and for this reason it is not recommended for use in children

CONTRAINDICATIONS

'Tenormin' is contraindicated in patients with second degree or third degree heart block. 'Tenormin' should not be used in patients with cardiogenic shock.

PRECAUTIONS

Special care should be taken with patients whose cardiac reserve is poor. Myocardial contractility must be maintained and signs of failure controlled with digitalis and diuretics.

One of the *pharmacological actions of 'Tenormin'* is to reduce heart rate. In the rare instances when symptoms may be attributable to the slow heart *rate, the dose may be reduced*

'Tenormin' modifies the tachycardia of hypoglycaemia

'Tenormin' may be used with caution in patients with chronic obstructive airways disease However, occasionally some increase in airways resistance may occur in asthmatic patients In contrast to non-selective betablockers, this bronchospasm may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

In patients suffering from ischaemic heart disease, as with other beta-blocking agents, treatment should not be discontinued abruptly.

Care should be taken in prescribing a beta-adrenoceptor *blocking drug with Class I antidysrhythmic* agents such as disopyramide.

Beta-adrenoceptor blocking drugs should be used with caution in combination with verapamil in [illegible]

[illegible]

Caution should be exercised when transferring [illegible]

[illegible]

Anaesthesia

[illegible]

Renal failure

[illegible]

ml/min/1.73 m² *(equivalent to serum creatinine* of 300-600 micromol/litre) the oral dose should be 50 mg

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